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THROMBOLYSIS WITH FIBRINOLYSIN (PLASMIN)—NEW THERAPEUTIC APPROACH TO THROMBOEMBOLISM

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Fifty-two patients with various forms of thromboembolic disease were treated by intravenous infusions of a preparation of fibrinolysin in dosages up to 90,000 fibrinolytic units (FU). The resulting increase in the fibrinolytic activity of the patient's plasma was demonstrated by laboratory determinations of the rate of dissolution of a standard fibrinogen-thrombin clot. When the dosages were between 40,000 and 50,000 FU, 92% of the recipients manifested an enhanced plasma fibrinolytic activity at some time after the infusion. Ten case histories illustrate the symptomatic relief that generally followed the infusion. Hemorrhagic complications have not occurred, and disturbances of the blood-coagulating factors were minimal as measured by prothrombin time, recalcification time, prothrombin content, proconvertin content, proaccelerin content, and fibrinogen content. Fever followed the infusion in 25 patients, and delayed allergic skin reactions occurred in 2; these were the most significant side-effects. The results encourage further trials in cases of thromboembolic disease of peripheral, cerebral, and coronary vessels.

Despite improved diagnostic and therapeutic techniques, thromboembolism maintains its unwelcome position as one of the major causes of medical morbidity and mortality. It has become apparent that the anticoagulant drugs do not provide a definitive answer to this problem. While the extension of existing thrombosis, or its recurrence, may be favorably influenced by these agents, the original thrombus remains. The organism is left to its own devices in dealing with this occlusive mass. Such devices rarely act with sufficient speed and intensity to prevent tissue damage, even though recanalization may be achieved eventually.

In recent years, therefore, much attention has been directed toward a class of materials grouped together under the term fibrinolytic agents. These compounds share the ability to promote the dissolution of the fibrin framework on which a thrombus is supported. By exerting fibrinolytic effects within the vascular system, such agents should be capable of acutely dissolving thrombotic material. The ability to achieve rapid thrombolysis, combined with anticoagulant drugs, would appear to constitute "ultimate therapy" in thromboembolic states.

Perhaps the first fibrinolytic agent to attract attention was streptokinase. This material, first demonstrated in the filtrates of beta-hemolytic streptococcic cultures by Tillett and Garner in 1933,[1] is still an object of active investigation. While fre-

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quently regarded as a fibrinolytic substance, streptokinase has no direct action on fibrin. Rather, it functions as an activator of the plasma proenzyme, profibrinolysin (plasminogen), either by direct action or by converting a plasma proactivator to an activator.[2] By such action, streptokinase converts profibrinolysin to the active fibrinolytic enzyme

TABLE 1.—*Composition of Patient Group, by Disease*

	Patients, No.	Infusions, No.
Active deep thrombophlebitis		
With pulmonary embolism	3	5
Without pulmonary embolism	15	16
Pulmonary embolism from unknown source	8	11
Arterial occlusion		
Cerebral thrombosis	12	13
Internal carotid thrombosis	2	3
Coronary thrombosis	1	1
Brachial arterial embolus	1	2
Radial arterial thrombosis	1	1
Popliteal arterial embolus	1	1
Retinal arterial thrombosis	1	1
Superficial thrombophlebitis	7	7
	52	61

fibrinolysin (plasmin). Therefore, the effect of streptokinase is dependent on the presence and concentration of profibrinolysin.

Unfortunately, inhibitors of streptokinase are present in a significant portion of the population, probably as a consequence of the ubiquity of streptococcic infections.[3] The presence of antistreptokinase factors in the plasma not only may increase the risk of allergic reaction but also would tend to limit the frequency and intensity of fibrinolytic activity which can be achieved by streptokinase infusion in the human body. The most purified preparations of streptokinase available still retain toxic potential and appear to provide an unreliable method for achieving plasma fibrinolytic activity in man at well-tolerated dosage levels.[4] Since both allergic and inhibitory phenomena are likely to be enhanced by streptokinase administration, the therapeutic value of this agent becomes subject to question.

Other workers have explored the use of the enzyme trypsin as a thrombolytic agent. This proteolytic enzyme not only can lyse fibrin directly but also serves as an activator of profibrinolysin.[5] However, the intravenous infusion of trypsin has not consistently led to the dissolution of thrombi in experimental animals or in man.[6] Furthermore, considerable antitryptic activity resides in both animal and human plasma.[7] Doses of trypsin which can overcome this inhibitor activity and produce reliable fibrinolytic effects also may have potent action against many of the protein components of plasma, including those necessary for blood coagulation.[7] These considerations appear to render intravenously given trypsin unsuitable as an agent for achieving acute dissolution of the intravascular clot in man.

As it became evident that streptokinase and trypsin had a number of theoretical and practical limitations as thrombolytic agents, interest became centered on fibrinolysin itself as a possible therapeutic weapon. While the presence of this intrinsic fibrinolytic agent in the blood of man and other mammalian species had been demonstrated before the turn of the century, only recently did technological advance permit its satisfactory isolation from human and bovine plasma. By modern biochemical procedures, profibrinolysin can be obtained from the globulin fraction of the plasma proteins.[8] Activation of this material to fibrinolysin is readily achieved by small amounts of streptokinase, which can be removed subsequently.

Since fibrinolysin has become available for investigational use, a number of important facts relating to it have become established. Unlike trypsin, intravenously given fibrinolysin does not attack a variety of plasma proteins with equivalent effect. Rather, it chooses fibrin as its major target of enzymatic activity.[9] This specificity of attack appears related to the fact that fibrin actually adsorbs fibrinolysin.[10] These qualities allow this agent to achieve satisfactory intravascular fibrinolytic activity in animals without disturbance of the coagulative mechanism over a wide dosage range.[12] Furthermore, several workers have shown that infusion of fibrinolysin will consistently dissolve experimentally produced arterial and venous thrombi in the dog and the rabbit.[13] Toxic reactions to effective intravenous doses of fibrinolysin in these experimental animals have been infrequent and minor.[13]

These observations have suggested that fibrinolysin may satisfy the major criteria for the ideal fibrinolytic agent, viz., the ability to achieve rapid liquefaction of intravascular clot without undue toxic effects.

In early 1957, a detailed study of the toxic and therapeutic effects of fibrinolysin in the human was begun at the District of Columbia General Hos-

TABLE 2.—*Incidence and Degree of Febrile Response to Fibrinolysin Infusion*

Peak Postinfusion Temperature Rise, Degrees Fahrenheit	Infusions, No.	Infusions, %
0-1	31	50.8
1-2	11	18.0
2-3	8	13.1
3-4	8	13.1
>4	3	5.0

pital. To date, 52 patients with various forms of thromboembolic disease have received one or more intravenous infusions of fibrinolysin. This preliminary report is a summary of the major observations made during this period of investigation.

Materials and Methods

Patients.—The 52 cases included in this study encompass all forms of thromboembolic disease

(table 1). All patients treated were inpatients at the District of Columbia General Hospital between February and December, 1957.

Fibrinolysin.—The profibrinolysin used in this study is a highly purified derivative of human plasma protein fraction 3. It is activated to fibrinolysin (Actase) with small amounts of purified streptokinase, after which the residual streptokinase is removed. The activated material is then lyophilized, in which form it is stable for several months at −4 C. One fibrinolytic unit of fibrinolysin has been defined as that amount of a standard preparation which will change the turbidity of a standard fibrinogen-thrombin clot by 50% in 10 minutes.

The dosage of fibrinolysin was gradually increased as the study progressed. Thirteen patients received infusions of 30,000 fibrinolytic units (FU); 19 patients, 40,000-50,000 FU; and 20 patients, 69,000-90,000 FU. Nine patients received two infusions on separate days, so that infusions totaled 61.

TABLE 3.—*Incidence of Fever Related to Extent of Thrombosis Present*

Thrombotic Disease*	Infusions, No.	Febrile Reactions No.	Febrile Reactions %
Major			
Active deep thrombophlebitis	21	13	
Pulmonary embolization	11	6	
Superficial thrombophlebitis	7	4	
Total major disease	39	23	59
Minor			
Cerebral thrombosis	13	4	
Internal carotid thrombosis	3	1	
Radial artery thrombosis	1	1	
Brachial artery embolus	2	1	
Popliteal artery embolus	1	0	
Coronary thrombosis	1	0	
Retinal artery thrombosis	1	0	
Total minor disease	22	7	32

* "Major" and "minor" refer to probable amount of thrombotic material present, not to functional consequences of thrombosis.

Plan of Study.—Fibrinolysin was dissolved immediately prior to use in 500 to 1,000 cc. of 5% dextrose in water. Intravenous infusion was then carried out over a two-to-four-hour period. Baseline and serial postinfusion blood samples were studied as follows: one-stage prothrombin time,[14] plasma recalcification time,[14] fibrinogen content,[15] and plasma fibrinolytic activity in all samples; prothrombin content,[16] factor V (proaccelerin),[16] and factor VII (proconvertin)[16] in all samples from 35 patients; and hematocrit value and white blood cell count before and 24 hours after infusion. Temperature, pulse rate, and blood pressure were measured at three-to-four-hour intervals in all patients for at least 24 hours after infusion. Urinalyses and electrocardiograms were obtained before and 24 hours after fibrinolysin infusion in all patients. In 18 patients electrocardiograms were also obtained during or shortly after infusion. The clinical course of each patient was carefully followed throughout hospitalization and at subsequent visits to the outpatient department.

Toxicity

Fever.—A temperature elevation of 1 F or more occurred in 49.2% of patients receiving fibrinolysin (table 2). The febrile reaction usually began 6 to 8 hours after infusion, reached an average peak of 2.9 F (range, 1.0-5.2) at 10 hours, and declined to normal within the next 10 hours. Approximately 25% of these patients experienced some chilliness or nausea at the peak of the febrile response.

Febrile response did not correlate, in either incidence or degree, with size of fibrinolysin dose or amount of fibrinolytic activity achieved in the plasma. However, the incidence of fever was significantly higher among those patients in whom extensive thrombotic material may be presumed to exist (table 3). No patient received medication designed to prevent or limit the febrile response. More recent experience had indicated that the febrile responses can be prevented or markedly ameliorated by aspirin-antihistaminic prophylaxis.

Blood Pressure and Pulse Rate.—No significant blood pressure deviations followed fibrinolysin infusion at any dosage level. Tachycardia occurred only in patients with pyrogenic reactions.

Allergy.—Two instances of allergic reaction developed on the third day after fibrinolysin infusion, one characterized by erythema at the site of infusion and the other by generalized urticaria. Both responded promptly to local measures and antihistamines.

Effects on Coagulation.—In the doses used, intravenously given fibrinolysin did not compromise the integrity of the coagulation mechanism. Prothrombin time and content, plasma recalcification time, and proconvertin and proaccelerin contents remained stable after infusion in the majority of patients (table 4). At no time interval did the average values for any of these factors fall below 90% of base-line values (table 5). A majority of

TABLE 4.—*Percentage of Patients Showing Abnormality in Blood Factors Three, Six, and Twenty-four Hours After Start of Fibrinolysin Infusion*

	3 Hr.	6 Hr.	24 Hr.
Prothrombin time, prolongation	42.4	44.1	40.3
Recalcification time, prolongation	30.8	29.3	40.4
Prothrombin content, depression	33.5	44.4	50.0
Proconvertin content, depression	36.7	21.2	36.7
Proaccelerin content, depression	26.7	37.1	25.0
Fibrinogen content, depression	64.5	53.1	37.9

TABLE 5.—*Average Change in Coagulation Parameters and Factors* Three, Six, and Twenty-four Hours After Start of Fibrinolysin Infusion†*

	3 Hr.	6 Hr.	24 Hr.
Prothrombin time, sec.	+0.3	+1.7	+2.7
Recalcification time, %	107.0	105.1	92.5
Prothrombin content, %	94.6	91.5	91.6
Proconvertin content, %	94.5	95.5	90.1
Proaccelerin content, %	94.3	91.4	97.8
Fibrinogen content, %	86.3	90.2	100.4

* Reported as % activity, taking base-line values as 100%.
† Values represent average of total group.

patients did show some depression of fibrinogen content at three and six hours after infusion. However, the average fibrinogen loss was small, and base-line values had been reached or exceeded in most patients by 24 hours after infusion. There was no statistically significant tendency toward greater loss of coagulation factors as fibrinolysin dosage was increased.

TABLE 6.—*Percentage of Patients with Enhanced Plasma Fibrinolytic Activity Three, Six, and Twenty-four Hours or at Any Time After Fibrinolysin Infusion**

Dosage, Fibrinolysin Units	Infusions, No.	3 Hr.	6 Hr.	24 Hr.	Any Time†
30,000	14	78.6	42.8	28.6	85.7
40,000-50,000	24	75.0	62.5	41.7	91.7
69,000-90,000	23	73.9	60.9	78.3	86.9
Total	61	75.4	57.4	52.5	88.5

*Enhanced activity is present when plasma would dissolve standard clot in 10% less time than that required by base-line plasma sample.
†Enhanced activity in at least one postinfusion sample.

These laboratory studies, indicating minimal disturbance of coagulation factors, correlated well with the clinical observation that no instance of hemorrhage was noted in any patient who received fibrinolysin, including 29 who were simultaneously receiving coumarin drugs or heparin. Possible "silent" internal hemorrhage appears excluded by the stability of the hematocrit values measured before (34.9%) and 24 hours after (34.3%) infusion.

Electrocardiogram.—In two patients electrocardiographic abnormalities were seen after fibrinolysin infusion. A 79-year-old woman with arteriosclerotic heart disease and mild cardiac decompensation developed atrial fibrillation 14 hours after fibrinolysin infusion, and a 27-year-old man with iliofemoral thrombophlebitis developed transient T-wave changes about 8 hours after infusion. In both patients, these changes occurred near the peak of significant febrile reactions.

Urinalysis.—No urinary sediment abnormalities occurred after fibrinolysin infusion. Transient, mild (1+, 2+) proteinuria occurred in 10 patients, all of whom had had febrile reactions to infusion.

Delayed Toxicity.—Periods of follow-up observation have extended from two weeks to eight months; no form of delayed toxicity has occurred.

Fibrinolytic Activity

The primary objective of intravenous fibrinolysin infusion is to achieve a level of plasma fibrinolytic activity which may be capable of dissolving an intravascular thrombus. Several methods can be used to detect such activity. The procedure used in this laboratory is a direct test of the ability of a plasma sample to dissolve a standard fibrinogen-thrombin clot. Increase in fibrinolytic activity is reflected by a more rapid lysis of the standard clot.

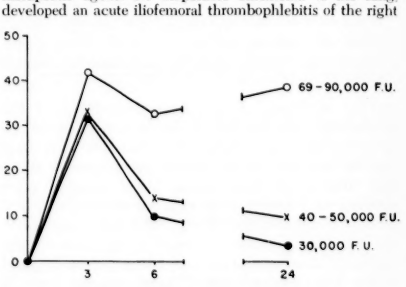
With this method it has been possible to demonstrate that fibrinolysin consistently produces a significant degree of fibrinolytic activity in the circulating plasma (table 6). The intensity and duration of fibrinolytic activity was a function of fibrinolysin dosage (see figure). At levels of 69,000 fibrinolytic units or more, high degrees of lytic activity are usually present for 6 to 8 hours and considerable activity frequently persists for 24 hours.

Therapeutic Observations

Deep Venous Thrombophlebitis.—Eighteen patients with deep venous thrombophlebitis involving the lower extremities received one or more infusions of fibrinolysin (table 1). Thirteen of these patients received anticoagulant therapy simultaneously or subsequently (see under Comment). Three patients in this group had suffered one or more pulmonary embolisms prior to fibrinolysin therapy.

Results of fibrinolysin infusion in this uncontrolled series have been consistently encouraging. While individual patients showed moderate variation in rapidity and degree of response, the over-all experience has included (1) loss of heat, tenderness and muscle turgidity, and significant decrease in leg size, by measurement, within 24 hours; (2) return of the involved area to its prephlebitic state within 72 hours after infusion; and (3) no recurrence of signs of phlebitis when ambulation was allowed. No pulmonary emboli occurred after fibrinolysin therapy. The following three case reports from this series illustrate the response of patients with deep venous thrombophlebitis.

CASE 1.—A 58-year-old man, who was receiving chemotherapeutic agents for inoperable carcinoma of the lung, developed an acute iliofemoral thrombophlebitis of the right



Average enhancement of plasma fibrinolytic activity after fibrinolysin infusion at three dosage levels. Percentage of increase (*vertical column*) of plasma fibrinolytic activity = $\frac{\text{(base-line lysis time)} - \text{(lysis time at x hours)}}{\text{(base-line lysis time)}} \times 100$

leg. The entire extremity became swollen, hot, and painful, with dilatation of superficial veins over the lower part of the leg. The patient was unable to walk. Therapy with bed rest and leg elevation was instituted. Anticoagulant drugs were withheld because of recent episodes of hemoptysis. After five days of such therapy, only slight improvement had occurred.

An intravenous infusion of 30,000 FU of fibrinolysin was carried out on the fifth day of his illness without evidence of toxicity. Twenty-four hours after infusion, the right leg had markedly decreased in size, averaging 3 cm. less by measurement in both calf and thigh. Heat and redness had subsided, and the patient tolerated deep palpation of the leg without pain. Two days after infusion, the extremity had returned to its prephlebitic state. The patient was ambulated 72 hours after infusion without recurrence of signs or symptoms. During a four-month period of observation, the leg has maintained its postinfusion improvement and the patient has continued to be ambulatory.

CASE 2.—A 45-year-old man developed a cramp-like pain in the right calf 11 days before admission. This subsided after a day of rest at home. Nine days before admission the calf pain returned and was accompanied by heat, slight swelling, and moderate tenderness. Over the next several days, the process appeared to improve. However, the morning of admission the right calf became acutely swollen, hot, and extremely tender to touch and ambulation was impossible.

Examination revealed a temperature of 100.8 F (38.2 C) and a pulse rate of 100 per minute. The right calf was exquisitely tender, reddened, and hot. There was marked turgidity of the calf musculature, and the superficial veins were dilated. Homans' sign was present. The right midcalf circumference was 2.5 cm. greater than the left.

Eight hours after admission, 69,000 FU of fibrinolysin was infused over a two-hour period without evidence of toxicity. Six hours after infusion, therapy with heparin and bishydroxycoumarin was begun. Nine hours after the fibrinolysin infusion, heat and turgidity of the calf were much decreased. Superficial vein dilatation had subsided, and deep palpation of the calf now produced only questionable discomfort. Twenty-four hours after infusion, improvement had continued. Measurements then disclosed an 0.8-cm. difference between the two midcalf areas. Residual pain was confined to a small area just posterior to the internal malleolus, where a tender segment of thrombosed superficial vein could be felt. Seventy-two hours after infusion this area was no longer tender, although the venous segment remained palpable. The patient was ambulated and anticoagulants were gradually discontinued. Follow-up examination one month later disclosed no recurrence of signs or symptoms of venous disease.

CASE 3.—A 67-year-old man with arteriosclerotic heart disease and chronic uremia developed marked swelling and tenderness of the left calf five days prior to admission. Two days before admission, the thigh also had become swollen and warm and calf swelling and tenderness had increased. Bed rest at home led to no improvement.

When the patient was admitted, the left leg showed a trace of pretibial edema and a turgid, quite tender left calf. The medial portion of the thigh was also firm, slightly tender, and warm. The left calf circumference was approximately 3.0 cm. greater than the right throughout, and the left thigh was approximately 2.5 cm. greater.

About 10 hours after admission, the patient received an infusion of 75,000 FU of fibrinolysin over a two-hour period. Heparin therapy was begun after completion of this infusion. Twenty-four hours later the turgidity, heat, and tenderness of both calf and thigh had subsided. The patient tolerated deep palpation with equivocal tenderness and moved the leg without pain. The leg had decreased approximately 2 cm. in average circumference in both calf and thigh.

By 48 hours after infusion, the leg showed no evidence of the phlebitic process. Heparin therapy was tapered over the next 36 hours, and the patient was considered ready for discharge insofar as the phlebitic episode was concerned. However, he remained in the hospital for further investigation of his renal status.

Pulmonary Embolism.—Eight patients with pulmonary embolism in whom no definite thrombotic source could be incriminated received fibrinolysin infusion within 72 hours of the embolic event. No untoward reaction, other than fever, followed infusion. In four patients a sequence of events suggesting that fibrinolysin therapy exerted some beneficial effect was noted. Criteria suggesting the influence of fibrinolysin included (1) rapid resolution of electrocardiographic abnormalities; (2) rapid relief of chest discomfort, tachypnea, and other symptoms and signs induced by embolization; and (3) interruption of a course of recurrent embolization which had not responded to anticoagulant therapy. Two representative cases are presented here.

CASE 4.—A 36-year-old man was admitted to hospital Dec. 9, 1957, because of sudden onset of dyspnea and hemoptysis. In May, 1953, a mitral valvulotomy had been performed for highly symptomatic mitral stenosis. The functional result had been excellent. After this surgery, the patient had remained consistently free of signs or symptoms of cardiac failure. However, atrial fibrillation had persisted despite several conversion attempts. Because of this, digitalization had not been interrupted.

Twelve hours before admission, the patient awoke with a paroxysm of nonproductive cough. He began to sweat profusely, felt weak, and developed dyspnea and orthopnea. Coughing paroxysms continued. Three hours after the onset of symptoms, brisk hemoptysis occurred. No chest pain developed. The hemoptysis and other symptoms persisted to the time of admission.

On admission, the patient was in acute respiratory distress, coughing frequently and producing moderate amounts of bright red blood. Blood pressure level was 110/80 mm. Hg, pulse rate 110 per minute and grossly irregular, and temperature 100 F (37.7 C). Expansion of the right hemithorax appeared diminished. Coarse breath sounds and fine rales were present in the right midlung field posteriorly. Anteriorly at the right base there were scattered rales and a questionable pleural friction rub. A few rales were present in the left base. The heart was slightly enlarged to the left. The second pulmonic and first mitral sounds were accentuated. An opening snap, a soft mid-diastolic murmur, and a grade-2 blowing systolic murmur were heard at the apex. No gallop sounds were present.

Roentgenogram of the chest showed moderate cardiomegaly, accentuation of hilar vascular shadows bilaterally, and a soft infiltration extending from the hilum into the right upper lobe. The white blood cell count was 9,800 per cubic millimeter with a slight shift to the left. An electrocardiogram showed atrial fibrillation, a vertical QRS axis, and an S-T vector compatible with "subendocardial ischemia." The venous pressure was normal. Findings on blood and sputum cultures proved negative.

Oxygen therapy was started, the patient was given sedatives, and digitalization was maintained. The following morning, some 12 hours after admission, the patient appeared critically ill. The temperature had risen to 102 F (39 C), the cardiac rate averaged 110 to 120 per minute, and marked tachypnea persisted. A loud pleural friction rub was now present over the anterior aspect of the right hemithorax, and numerous rales were heard scattered throughout the right lung. The left lung was clear. Hemoptysis continued, though at a less brisk pace. Intravenous heparin therapy was begun at this time. One hour later, 75,000 FU of fibrinolysin was infused intravenously over a period of two hours.

Three hours after the start of this infusion, the patient had obviously improved. His tachypnea had subsided, and the cardiac rate had decreased to 80. The second pulmonic sound had decreased in intensity. The temperature rose to 104 F (40 C) 12 hours after infusion, then rapidly fell to normal for the first time since admission.

Twenty-four hours after infusion, an electrocardiogram showed slowing of the ventricular rate, disappearance of S-T changes, and leftward shift of the terminal QRS forces. The pleural friction rub was less striking, and the right hemithorax was moving well. Forty-eight hours after infusion, the patient was asymptomatic. The right lung was now completely clear on examination. The hemoptysis had ceased and did not recur.

Chest x-ray on the third hospital day showed decrease in the perihilar accentuation and clear lung fields. The patient was ambulated on the fourth day, and anticoagulant therapy was continued for a total of 10 days.

CASE 5.—A 40-year-old woman entered the hospital because of the sudden onset of pleuritic chest pain, dyspnea, and hemoptysis. Two weeks prior to admission, the patient had had a total hysterectomy for uterine fibroids. The operation and recovery period had been uneventful, and the patient was discharged on the 10th postoperative day.

The day prior to admission, the patient suddenly developed pleuritic pain in the lateral and anterior aspects of the left hemithorax and moderate dyspnea. The pain persisted throughout the day and was still present the following morning, when the patient coughed up a small amount of bright red blood.

On her admission, blood pressure level was 120/90 mm. Hg, pulse rate 96 per minute, temperature 99 F (37.2 C), and respiratory rate 20 per minute. Dulness and a scattering of rales were present at the left lung base. The heart on examination was unremarkable, and the extremities showed no evidence of venous disease. Pelvic examination revealed some tenderness of the vaginal cuff. The electrocardiogram showed a sinus tachycardia. Chest x-ray demonstrated a zone of soft infiltration in the left lower lobe.

The patient was placed on therapy with heparin and a coumarin derivative. By the following day, she appeared improved and hemoptysis had ceased. On the third hospital day, however, the patient felt "uneasy" and had several tachypneic episodes. Examination now revealed rales at the right base, as well as at the left. The temperature rose to 100 F (37.7 C). Findings on sputum smear and culture were negative, as were those on blood culture. On her fourth hospital day, mild pleuritic pain was present on the left side and scattered rales were audible at the left base but the temperature had returned to normal. The electrocardiogram showed no alternation.

On the sixth hospital day, the patient had a sudden recurrence of pleuritic pain in the left anterior part of the chest, with renewal of dyspnea. Physical examination revealed rales throughout the lower left lobe posteriorly and a pleural rub laterally. The temperature rose to 101 F (38.3 C). The following day, the patient again had slight hemoptysis. A chest roentgenogram revealed an increase in the area of density at the left base. At this juncture, 46,000 FU of fibrinolysin was infused over a period of three hours. A temperature elevation of 1 F followed infusion. However, within 18 hours the patient's temperature had descended to 99.2 F (37.3 C). Twenty-four hours after the infusion, chest pain was absent and the patient was able to inspire deeply without pain. The pleural rub was no longer audible.

Since the recurrent embolization despite anticoagulant therapy suggested the possible necessity of inferior vena caval ligation, the patient received a second fibrinolysin infusion of 69,000 FU 36 hours after the first. Again a 1 F temperature elevation occurred. After the second fibrinolysin infusion, the patient remained free of symptoms. During the remainder of her hospital stay, she had no chest pain. Serial chest roentgenograms showed gradual resolution of the infiltration at the left base in the form of two linear scars. The right base remained clear. Four days after the second infusion, the patient was ambulated and anticoagulant therapy was tapered. The patient was seen in the clinic three weeks after discharge. At that time she remained symptom-free.

Peripheral Arterial Occlusion.—Experience in this study with acute peripheral arterial occlusion has been limited to three patients. One patient with embolic occlusion of the left brachial artery received fibrinolysin infusion six days after admission with no apparent benefit. Another patient with occlusion of the left radial artery secondary to trauma received fibrinolysin eight days after onset of occlusion without response. The third patient received this agent 48 hours after an embolic occlusion of the left popliteal artery. Heparin therapy and sympathetic blockade over a two-day period did not relieve the pallor, coolness, and paresthesia in the lower part of the leg. Twelve hours after fibrinolysin infusion, the temperature and color of this leg had markedly improved and paresthesia had subsided. The improvement was maintained over a four-day period of observation.

Cerebral Arterial Occlusion.—Despite multiple problems in evaluation, the paucity of effective therapeutic methods for dealing with cerebral thrombosis offers ample justification for trial of thrombolytic agents. Such therapy may be especially helpful in the syndromes of basilar or internal carotid artery insufficiency, if present concepts regarding their pathogenesis are valid.

Any criteria for differentiating thrombosis from hemorrhage are subject to considerable error. The arbitrary criteria used in this study have been (1) onset of neurological signs compatible with cerebral thrombosis without convulsion, syncope, or headache, (2) blood pressure on admission not exceeding 160 systolic and 100 mm. Hg diastolic, and (3) normal pressure, protein level, and cell count of spinal fluid.

Fourteen patients with cerebral or internal carotid artery thrombosis received infusions of fibrinolysin. In only four instances was this given within 24 hours of the onset of symptoms. In all other cases, the neurological deficit had been stable for at least three days prior to infusion. Seven patients showed some degree of objective neurological improvement (return of speech and movement) within the 24 hours after infusion. Such improvement was transient in three patients and maintained in the other four. Seven patients had no unusual degree of improvement within 24 hours after infusion.

Six patients in this group ultimately died, including three who had shown "acute improvement" and three who had not. Two of the "improved" patients died of causes other than cerebrovascular disease; the other four deaths appeared directly related to the occlusive disease. Postmortem examination was obtained in three patients. Areas of cerebral soften-

ing, without demonstrable thrombotic arterial occlusion, were found in each case. No intracerebral hemorrhages were noted.

While these few uncontrolled observations provide no basis for conclusions regarding the therapeutic value of fibrinolysin in a process as unpredictable as cerebral thrombotic disease, they do suggest the safety of such therapy. Two representative cases in which there was "acute improvement" are presented here.

CASE 6.—A 51-year-old man entered the hospital on Aug. 7, 1957, for neurological evaluation. One year before admission he had had a syncopal episode. Over the succeeding months he had suffered recurrent left frontal headaches and transient ptosis of the left eyelid. Physical examination was negative, aside from indicating loss of the left corneal reflex. A carotid arteriogram on Aug. 9 demonstrated a large berry aneurysm just above the bifurcation of the left internal carotid artery.

On Aug. 14, a Selverstone clamp was applied to the left common carotid artery in the neck. Gradual occlusion was carried forward daily. By Aug. 20, the artery had been totally occluded. The patient experienced no neurological symptoms after total occlusion. On Aug. 21, the patient was taken to the operating room and the clamp removed. No pulsation was palpable beyond the site of the clamp, suggesting distal thrombotic occlusion. Ligatures were placed above and below the clamp site, and the patient was returned to the recovery room. Some 30 minutes later, the patient became unresponsive and developed a complete right-sided hemiparesis. The ligatures were immediately removed from the carotid artery. No improvement resulted, but it was noted that some pulsation was now present in the artery above the clamp site. The impression of the neurology service was that embolization had occurred from the clot in the carotid artery above the clamp, a known complication of this procedure. Lumbar puncture was negative.

The patient was placed on therapy with intravenously given heparin immediately. For the next 36 hours, the patient remained unresponsive. He exhibited marked restlessness and was incontinent. No movement returned to the right arm or leg, and speech was limited to occasional grunting. At this point, 46,000 FU of fibrinolysin was infused over a four-hour period. Heparin therapy was discontinued at this time. Seven hours after infusion, the patient was first noted to be moving the right arm and leg. His marked restlessness had subsided and bowel control had returned. He was still unable to speak but was able to understand commands for the first time since operation. At 18 hours after infusion, motion had returned to all muscle groups on the involved side save the fingers and toes, and he was able to take nourishment orally.

A second infusion of 46,000 FU was carried out 21 hours after the first. Twenty hours later, movement had returned to the fingers and toes. He ate without difficulty and attempted to talk, but could not form words accurately. Heparin therapy was now resumed.

Thereafter, his condition steadily improved. Seven days after the initial infusion, the patient was ambulatory, although the right leg was weak. The right arm and hand were weak, but the patient could employ them usefully. Over the next several weeks, a program of physical and speech therapy led to progressive improvement.

Three months after the hemiparetic incident, the patient had excellent strength in the arm and leg and had regained satisfactory speech. Further neurosurgical attack on the aneurysm was contemplated.

CASE 7.—A 69-year-old man had developed a right-sided hemiparesis five years prior to admission, believed due to cerebral thrombosis, from which he had made a good functional recovery. Two days prior to admission, there was a sudden increase in right-sided weakness. The patient was unable to use the fingers of the right hand, and had poor movement at the wrist and elbow. There was also difficulty in ambulation because of marked weakness of the right toes, ankle, and knee.

Fibrinolysin infusion (46,000 FU) was carried out six hours after admission. Eighteen hours after infusion, the patient was able to clench his fist and hold objects in the hand (such as kitchen utensils, coffee cup) for the first time in three days. Ambulation was again satisfactory and ability to move the toes had returned. The improvement was maintained during 10 days of observation.

Coronary Thrombosis.—Intensive investigation in patients with coronary thrombosis has been delayed until further studies confirm that febrile responses can be prevented or adequately controlled. The present series includes only one such patient.

CASE 8.—A 47-year-old man entered the hospital on Oct. 8, 1957, because of progressively more frequent, severe, and prolonged episodes of substernal chest pain. The patient had a prior history of excellent health.

Seven days before admission, while at work, he developed a "burning" abdominal pain which radiated upward beneath the sternum and was accompanied by shortness of breath. This episode subsided within five minutes. Six days before admission, three identical episodes occurred at work. The following day, while he was at home in the bath tub, pain developed which lasted 15 minutes and was associated with generalized weakness. Four days before admission, four more episodes of pain occurred, three of these while at rest. Each lasted less than five minutes. The following day, while he was resting in the evening, the patient had a very severe episode of "tight, squeezing" epigastric and substernal pain which lasted almost an hour and was accompanied by sweating, apprehension, and mild dyspnea. The patient awoke the next morning with a recurrence of identical pain, which again persisted for more than an hour. When the pain had subsided, the patient was brought to the hospital.

Physical examination on admission revealed a blood pressure level of 130/90 mm. Hg, pulse of 72 per minute, and normal temperature. The fundi were unremarkable. The lungs were clear. The heart was not enlarged, and no murmurs or abnormal sounds were present. Remainder of the examination was within normal limits.

White blood cell count, hematocrit value, and erythrocyte sedimentation rate were within normal limits. The serum amylase level was normal. The chest roentgenogram was within normal limits. An electrocardiogram showed borderline evidence of left ventricular hypertrophy and a T vector indicative of acute anterolateral myocardial ischemia.

A diagnosis of "march" angina or "impending myocardial infarction" was made, and therapy was begun with heparin and bishydroxycoumarin. He had another short episode of substernal discomfort some eight hours after entry.

Twenty-four hours after admission, the electrocardiogram was unchanged. Physical examination remained unremarkable. Temperature, white blood cell count, and sedimentation rate remained normal. The patient received a two-hour infusion of 69,000 FU of fibrinolysin. Over the next 24 hours, temperature, pulse, and blood pressure remained stable and pain did not recur.

During the third hospital day, the patient remained asymptomatic. The electrocardiogram showed definite change, with rotation of the T vector toward normal and a decrease in T-wave amplitude. On the fourth hospital day, an episode of mild substernal discomfort occurred, lasting perhaps 30 minutes. The electrocardiogram showed no change. On the fifth through the eighth day, the patient was asymptomatic, aside from a momentary "flash" of epigastric

discomfort on the sixth and seventh days. Serial electrocardiograms showed a gradual return of the T vector and amplitude toward normal during this period.

The patient had no pain during the following 26 days of hospitalization. The electrocardiogram had reverted completely to normal by the ninth hospital day. At no time did fever, leukocytosis, or sedimentation rate elevation appear. During the third week a program of progressive ambulation was begun. Anticoagulant therapy was maintained throughout hospitalization and was continued on an outpatient basis. The patient has now remained asymptomatic for almost three months. His electrocardiogram continues to be within normal limits.

Superficial Thrombophlebitis.—Patients with superficial thrombophlebitis provide a valuable area for study, since this is one thrombotic state in which the thrombus can be observed directly. It is from this small group that we have derived the most objective evidence of the thrombolytic abilities of fibrinolysin.

Seven patients with superficial thrombophlebitis have received fibrinolysin intravenously. Three patients in this group had had their thrombotic process for more than seven days. In these, no beneficial effects were noted. In the other four cases, evidence suggesting thrombolysis by fibrinolysin appeared. Two of these are reported here.

CASE 9.—A 59-year-old man had had a cardiac catheterization performed via the left basilic vein on Dec. 12, 1957. The procedure was without incident. On Dec. 16, the patient complained of severe pain in the left arm. Examination revealed a palpable cord 10 cm. in length along the course of the basilic vein. This was surrounded by an area of erythema, heat, and marked tenderness. The arm was elevated and ace bandages and warm packs were applied.

Twenty-four hours later there had been no discernible improvement. Fibrinolysin (75,000 FU) was given intravenously in the opposite arm over a two-hour period. By eight hours after infusion, the erythema and heat surrounding the involved vein had decreased and the patient tolerated deep palpation of the arm with minimal discomfort. Twenty-four hours after infusion, all evidence of acute inflammation had disappeared. The venous cord was now palpable for a distance of 4 cm., representing a 6-cm. decrease in length since infusion. Minimal tenderness to palpation remained over the distal part of this cord. The patient could use the arm without discomfort.

All tenderness over the vein had subsided by the fourth day. Observation for eight days after infusion showed no return of symptoms or signs. A 4-cm. zone of clot still remained palpable at the end of this period.

CASE 10.—A 56-year-old man was referred to me because of multiple painful thromboses in the superficial veins of both arms. During two prior weeks of hospitalization various diagnostic and therapeutic procedures had required numerous venipunctures, many of which had been followed by development of local superficial phlebitis. At the time of examination, two areas of active phlebitis were present. A thrombosed segment of vein some 5 cm. long over the right forearm had followed a venipuncture 48 hours prior. In the right antecubital area, a thrombosed segment measuring 3.5 cm. had followed a venipuncture 24 hours prior. Both thrombi were paralleled by an area of erythema, heat, and tenderness which extended above and below them for a short distance. Six other areas of venous thrombosis were present in the forearms and antecubital fossae. These showed no evidence of inflammation, ranged from 2 to 5 cm. in length, and were one to two weeks old.

Fibrinolysin (46,000 FU) was infused via an uninvolved vein in the right forearm. Twenty-four hours after infusion, the two "active" areas no longer showed evidence of inflammation. The palpable thrombus in each had disappeared, and blood could be withdrawn easily from both. The other zones of palpable thrombus showed no change. Improvement in the areas mentioned was maintained over an observation period of six days. Hematological evaluation of this patient disclosed no cause for his "thrombotic tendency" to venipuncture.

Comment

The availability of an agent of low toxicity which is capable of acutely dissolving intravascular clot would represent a major advance in the therapy of thromboembolic disease. On the basis of the studies reported above, one is justified in cautiously suggesting that fibrinolysin (plasmin) may be such an agent.

Promising qualities of fibrinolysin demonstrated by these investigations include the following observations: 1. The ability of the material to produce an active intravascular fibrinolytic system in the majority of patients. At the higher dosage levels, significant plasma fibrinolytic activity is frequently maintained for at least 24 hours. 2. The low toxicity of fibrinolysin infusion, which is limited primarily to pyrogenicity at the dosages employed. Hemorrhagic complications have not occurred. Anticoagulant drugs can be safely used simultaneously. Laboratory studies indicate that a wide margin of safety exists between fibrinolysin dosages which can enhance plasma fibrinolytic activity and those which may impair coagulation. Embolization has not complicated the therapy of venous thrombotic disease. Allergic reactions have been rare and mild. 3. The clinical results after fibrinolysin infusion, which have been consistently encouraging in terms of its apparent ability to dissolve a recently acquired intravascular clot.

These observations constitute an impressive array of "plus signs" on the fibrinolysin balance sheet. However, at least four major facets of fibrinolysin therapy appear to require further study: (1) certain aspects of fibrinolysin toxicity; (2) establishment of proper dosage schedules; (3) accurate estimation of the value of fibrinolysin in various thromboembolic states; and (4) the need for anticoagulant therapy after acute thrombolysis.

Toxicity.—The problems of toxicity, at the dosages used in this study, appear restricted primarily to elucidation of the cause of the febrile reaction to fibrinolysin. Present data indicate that profibrinolysin is not pyrogenic. Since no streptokinase activity can be demonstrated in the fibrinolysin material itself, streptokinase cannot be incriminated. Therefore, fever must stem from either pyrogenic, nonstreptokinase residuals of the activation process or from the actions of fibrinolysin itself within the body. The more frequent occurrence of fever in patients with extensive thrombotic zones suggests that febrile reactions may result from the protein

fractions released when fibrinolysin acts upon fibrin. Whatever its cause, the danger of pyrogenicity presently limits the application of this material in such critical states as coronary thrombosis. Further study regarding its etiology and the ability of aspirin-antihistaminic prophylaxis to control fever is therefore of considerable importance.

While minimal toxicity followed fibrinolysin infusion in this study, it is important to recognize that the observations regarding toxicity did not extend beyond doses of 90,000 FU. Significant depletion of coagulation factors, and perhaps other toxic effects, may occur at higher dosage levels. Since fibrinogen appears to be the most sensitive of the clotting factors to fibrinolysin infusion, qualitative measurement of fibrinogen before and after infusion would enhance the safety of fibrinolysin therapy. Presently, such measurement appears mandatory if dosages above 90,000 FU are employed.

Proper Dosage Schedules.—Determination of the ideal fibrinolysin dosage in various thrombotic states will require systematic study of large patient groups. The present investigations have indicated that considerable plasma fibrinolytic activity can be maintained for 24 hours in patients receiving 69,000 units or above. However, it is not known whether demonstrable plasma fibrinolytic activity must be achieved and maintained to bring about the dissolution of intravascular clot. In view of the strong adsorptive capacity of fibrin for fibrinolysin,[10] it is quite possible that fibrinolysin may exert considerable local effect upon a clot in the absence of demonstrable plasma fibrinolytic activity. Therefore, small, repeated doses of fibrinolysin may prove as efficacious as single, larger infusions.

It is equally possible that local factors may prevent access of fibrinolysin to a clot in some cases and lead to therapeutic failure, even in the presence of marked plasma fibrinolytic activity. Therefore, dosage of fibrinolysin will remain largely empirical until further experience permits adequate correlation between clinical effect and level of plasma fibrinolytic activity.

Therapeutic Value of Fibrinolysin.—Accurate estimation of the therapeutic value of fibrinolysin in various thromboembolic disorders poses a challenge of considerable magnitude. The complexity of such evaluation stems from our present inability to define with certainty the pathogenesis, diagnosis, and prognosis of most forms of vascular occlusion. For example, the consequences of coronary occlusion are identical whether the pathogenic basis for occlusion is thrombosis, subintimal hemorrhage, or embolization of atheromatous material. Obviously, fibrinolysin could not be expected to restore vascular continuity if either of the latter two mechanisms are operative. In cerebrovascular insults, the pathogenic possibilities are even greater.

Regarding diagnostic uncertainty, the problems involved in the precise diagnosis of pulmonary embolism or deep venous thrombosis are widely appreciated. The same lack of precision applies to prognosis, for thrombotic states are notoriously capricious in their "natural course." Such variability demands that considerable caution be exercised in attributing improvement to any therapeutic agent. The problem of prognosis is further complicated by the fact that there may be wide variation in the degree of functional return which can be expected in tissues sensitive to short periods of nutrient lack, even if thrombotic occlusion is totally relieved.

These multiple problems are not new. The complexities of evaluating agents used in thromboembolic disorders are vividly in evidence today in the form of the controversy which still rages regarding the value of the anticoagulant drugs in many conditions. As with the anticoagulant drugs, reliable evidence regarding the therapeutic value of fibrinolysin in most forms of thromboembolism will require large, controlled series. However, it should be recognized that "controlled" fibrinolysin series will not be valid unless attention is paid to another critical variable; namely, the age of the thrombotic process. In animal studies,[13] Cliffton and Ambrus have found that fibrinolysin is highly successful in dissolving intravascular clot as long as three days after formation. Beyond this point, experimental thrombi appear relatively resistant to fibrinolysin. Since animal studies involve artificial situations in which considerable vessel-wall trauma accompanies thrombosis, it is questionable whether such data can be applied directly to human thrombotic disease. However, it is clear that fibrinolysin "success" or "failure" will have to be interpreted with due regard to the probable structure of a clot at the time thrombolysis is attempted.

Need for Anticoagulant Therapy After Acute Thrombolysis.—Animal studies have suggested that rethrombosis after successful clot dissolution may occur when fibrinolysin is used alone but can be prevented when heparin is used concurrently.[12] Therefore, it appears that anticoagulant drugs should be used to avoid rethrombosis in all patients, unless circumstances clearly indicate that the factors which led to thrombosis have subsided.

This discussion has made it plain that the therapeutic evaluation of fibrinolysin will not be a simple task. While the results of these preliminary studies provide a firm basis for optimism regarding fibrinolysin, excessive enthusiasm should be avoided until further investigation has been completed. If the fibrinolytic agents are to be employed with maximum safety and benefit, therapeutic impatience must be tempered by sufficient scientific skepticism to delay widespread employment of these agents until an instructive body of controlled data can be accumulated.

Summary

A pilot study of the effects of intravenously given fibrinolysin (plasmin) has been carried out in 52 patients with various forms of thromboembolic disease. Toxicity, fibrinolytic activity achieved in the plasma, and therapeutic results were carefully evaluated.

In the doses used, toxicity of the agent appears limited to pyrogenicity, which was encountered in 49.2% of the patients. The mechanism of this response has not been defined. Two instances of delayed allergic skin reactions were noted. No embolic events have followed fibrinolysin infusion. Serial study of coagulation factors after infusion of fibrinolysin showed no clinically significant derangement of the coagulative process. No hemorrhagic phenomena were encountered in any patient, including 29 who were simultaneously receiving anticoagulant drugs.

Fibrinolytic activity of the plasma was consistently enhanced by fibrinolysin infusion. The intensity and duration of such activity paralleled total fibrinolysin dosage.

While the therapeutic results observed after infusion of fibrinolysin in several varieties of thromboembolic disease were encouraging, firm conclusions regarding its therapeutic value cannot be drawn from this pilot study and must await completion of large-scale controlled studies. However, the observations reported here do justify a cautious optimism that fibrinolysin may prove a safe and effective agent for achieving acute lysis of intravascular clot.

District of Columbia General Hospital, 19th and E streets S. E. (3).

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SCHOOL HEALTH.—One of the first things that will bring about a mutual understanding between school health and public health is a policy on communicable disease control. A complete and satisfactory agreement can be made with regard to local control of communicable diseases in a joint meeting with the school health committee of the County Medical Society, local health officers and the director of school health. . . . In planning a health education program, public schools and public health agencies should join with other agencies and make it a community project. A community health council organized by all official and non-official agencies in the community may serve as a clearing-house for all community health education program planning. Newer methods of health education can be developed and put into action when the community agencies work together.—A. E. Hill, M.D., M.P.H., Correlation Between School Health and Public Health, *The Journal of School Health*, May, 1958.

THROMBOLYSIS WITH FIBRINOLYSIN IN CEREBRAL ARTERIAL OCCLUSION

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Three patients with hemiplegia were treated by the slow intravenous infusion of fibrinolysin. The site of occlusion of the cerebral vessels was located in each case by arteriography. In one case the angiograms clearly showed nonfilling of the middle cerebral group of arteries before treatment, while on the eighth day after beginning treatment good filling of the middle cerebral vessels was obtained. This patient showed the most favorable results. The history of rheumatic heart disease and the fact that treatment was commenced within six hours after the onset of symptoms suggest that the lesion was caused by an embolus originating in the fibrillating left atrium and that the embolus was a fresh thrombus most susceptible to the lytic agent. No detrimental effects that could be ascribed either to the diagnostic angiography or to the administration of fibrinolysin were observed in these patients.

The most promising therapy for thrombotic occlusion of any vessel supplying the brain will probably be immediate solution of the clot by a parenterally administered agent. A surgically directed approach to the problem may be frustrated by the increasingly apparent complexities of vascular thrombosis. The appearance of symptoms may depend on complicated relationships between anastomotic channels. There is increasing evidence to make us speculate that a hemiplegia resulting from an apparent angiographically demonstrated thrombosis of the carotid artery, or of its cerebral branches, may actually result from the final thrombotic closure or stenosis of a vital collateral vessel elsewhere that is compensating for a long-standing obliterated proximal channel. Although transient neurological deficits may be related to alterations of the general systemic blood pressure, on which the stability of the collateral circulation depends, the more persistent and complete deficits are more likely the result of a final strategic thrombosis or other form of occlusion. Whatever might be done by the surgeon electively for lesser symptoms when the site of thrombosis or stenosis is demonstrable, in the presence of a severe neurological deficit, only the immediate elimination of the thrombus is likely to be of benefit. It is not believed practical that this can be accomplished surgically in the majority of instances.

There have been many reports in recent years of angiographically proved cases of carotid or major cerebral artery thrombosis.[1] Several workers have undertaken a surgical approach to the problem. Strully and associates[2] performed an incomplete thromboendarterectomy in 1953 in a patient with signs of aphasia and visual disturbance. They speculated that, under more favorable circumstances, the procedure might be effective. We have recently observed such a satisfactory complete removal of the thrombus within 24 hours of the appearance of hemiplegia and aphasia. Although vigorous flow was at least temporarily reestablished, the patient obtained no improvement. We have witnessed marked improvement after carotid thromboendarterectomy in a case of partial aphasia and hemiparesis; however, we cannot be certain that the surgery was responsible. Arnstein[3] is more enthusiastic about this procedure, although only 2 of his 10 patients would appear to have been radically improved after total deficit. Eastcott and associates,[4] Lin and co-workers,[5] Denman and associates,[6] and others have attempted to remedy either minor or recurrent episodes of neurological deficit by various other techniques, generally consisting of a vascular bridging graft or resection of the diseased arterial carotid segment. Although some improvement has been obtained under these circumstances, there has not yet been reported a patient with hemiplegia or global deficit who has made dramatic recovery after one of these procedures. Some lesser degree of recovery is to be expected without intervention. In this respect, Jackson[7] has recently demonstrated how, in two cases of improvement, the supposedly restored channel was proved to be obliterated at reexploration or angiography. In addition, surgery may actually interfere with the collateral if, unwittingly, the external carotid artery is kept from its function of supplying flow via the ophthalmic artery to the carotid, as shown by Vaernet.[8]

It is our feeling that the results of these procedures are not very encouraging, particularly under the circumstances of global deficit. With minor deficits or recurrent episodes, it is very likely

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that, in conjunction with anticoagulants, they offer some therapeutic and prophylactic promise. In the severe cases, the principal handicap inherent in this technique is the poorly tolerated delay between the appearance of symptoms and the removal of the thrombus. As demonstrated by Denny-Brown and Meyer,[9] this critical period must be very short before the changes in the damaged area of the brain become irreversible. This time is ordinarily consumed in the obligatory delay required for consultation between family physician and specialist, transportation, diagnostic angiography, and preparation for surgery. What has been needed is an agent, known to be effective in reversing thrombosis, which can be administered immediately on the appearance of symptoms by the first physician to arrive on the scene. Needless to say, the applicability of such a drug in the smaller vessel thromboses is enormous. It is hoped that in this study, in which the enzyme fibrinolysin has been used, there may be some promise of such an agent.

Fibrinolysin (plasmin)[10] is a naturally occurring proteolytic enzyme of plasma. Purified human plasminogen or profibrinolysin, its precursor, may be spontaneously activated in vivo to fibrinolysin or in vitro by urokinase (an enzyme obtained from urine). The effect of fibrinolysin, as demonstrated by many workers,[11] is the dissolution of vascular thrombi. This drug has been used clinically in the three patients reported here. Particular attention is invited to the third case.

Report of Cases

Case 1.—A 75-year-old woman, right-handed, was admitted to the hospital on Sept. 6, 1957, because of the abrupt appearance of hemiplegia of the right side and inability to speak. She was known to have hypertension of many years' duration and had required recent treatment for dyspnea and cystitis.

Physical Examination.—The patient aroused easily but could not speak and did not comprehend. A complete spastic hemiplegia on the right side was evident, with increased deep tendon reflexes and ipsilateral Babinski's signs. There was a moderate supranuclear facial weakness on the right. A resting alternating tremor of the left hand and forearm was observed. The carotid pulsations on the left varied on repeated examinations. Cardiac enlargement and a systolic apical murmur were noted. The blood pressure was 180/90 mm. Hg.

Laboratory Data.—The blood cell count was normal. Urinalysis revealed 1+ albumin, 6-10 white blood cells, 80-120 red blood cells, and bacteria. A left carotid arteriogram performed on Sept. 12, 1957, demonstrated nonfilling of the internal carotid artery beyond the bifurcation of the common carotid (fig. 1A).

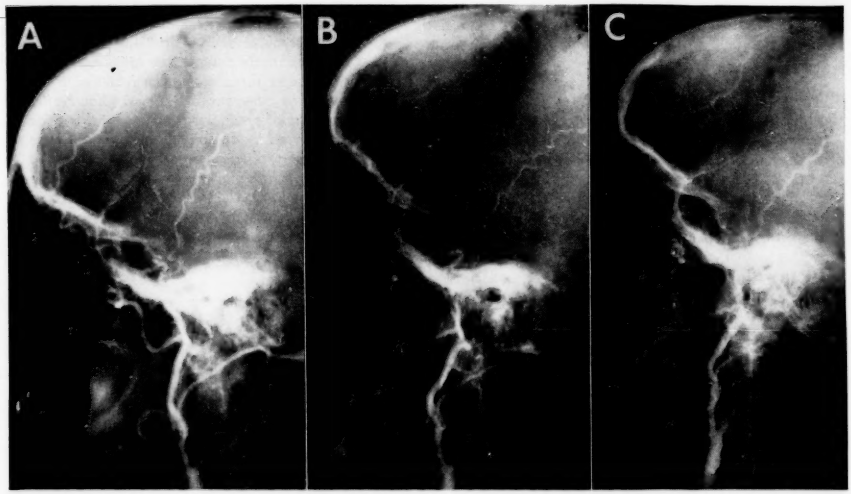

Fig. 1 (case 1).—*A*, arteriogram showing thrombosis of internal carotid artery at bifurcation of common carotid. *B*, evidence of partial clearing of internal carotid after six days of therapy. *C*, slight further clearing after six additional days of therapy.

Course.—On the same day, 50,000 units of fibrinolysin was given intravenously in 300 cc. of isotonic sodium chloride solution over a three-hour period. Simultaneously, 25,000 units in 100 cc. was given after one hour, over a 15-minute period, into the left carotid artery. This was repeated on three of the next four days. One injection of 200 mg. of heparin was administered on the day no fibrinolysin was given. A second left carotid arteriogram taken on Sept. 16, 1957, showed an incomplete 2-cm. column of dye in the proximal internal carotid (fig. 1*B*). Accordingly, 75,000 units of fibrinolysin was given daily, intravenously, in 500 cc. of isotonic sodium chloride solution over a two-hour period for the following six days. On Sept. 24, 1957, another

left carotid arteriogram showed slight further change (fig. 1C). No hypotensive effects of the drug were observed in this patient. There was some elevation of temperature, which ranged between 101 and 102 F (38.3 and 38.7 C), but this may have been due to chronic cystitis. The patient showed no improvement of her hemiplegia or aphasia. She appeared more alert, however, and was able to take oral feedings better after the course of treatment.

CASE 2.—A 52-year-old right-handed man was admitted to the hospital on Sept. 28, 1957, because of progressive hemiparesis of the left side. About one hour prior to admission, he noted weakness of the left lower extremity, which rapidly became complete. He had been in good health prior to this illness.

Physical Examination.—The patient was alert but somewhat facetious. There was a complete, slightly spastic paralysis of the left lower extremity. The left upper extremity was weak and much more spastic than the lower, with most involvement proximally. The deep tendon reflexes were hyperactive on the left. A Babinski's plantar reflex was obtained on the left. Findings in the general physical examination were within normal limits. The blood pressure was 130/80 mm. Hg, and the pulse rate was 90 per minute and regular.

Laboratory Data.—Blood cell count and findings on urinalysis were normal. A right carotid arteriogram performed six hours after admission demonstrated occlusion of the anterior cerebral artery at the point of bifurcation into the pericallosal and callosomarginal vessels (fig. 2).

Course.—Immediately after angiography, the patient received, intravenously, 100,000 units of fibrinolysin in 50 cc. of isotonic sodium chloride solution over a two-minute period. On each of the following five days, an infusion of 100,000 units was given in 500 cc. over a two-hour period. On Oct. 3, 1957, angiography failed to reveal any further filling of the anterior cerebral artery. During this period, a progression to a complete hemiplegia of the left side was noted. This was associated with a tendency to ignore the paralyzed limb and a mild hypalgesia over the left side of the body, as well as defective proprioception. These sensory findings gradually disappeared as the patient became aware of his deficit. In addition, there was noted a disappearance of the spasticity of the left upper extremity and an occasional demonstration of ability to extend the left lower extremity when supported by the examiner. During the course of therapy, a sustained temperature elevation of 102 to 103 F (38.7 to 39.4 C) was observed. This reverted to normal after cessation of the enzyme administration. A solitary hypotensive episode with a blood pressure reading of 90/40 mm. Hg was seen on the fifth day of treatment.

CASE 3.—The patient, a 50-year-old right-handed woman, was admitted to the hospital on Oct. 22, 1957, after falling from bed on attempting to arise that morning. A paralysis of her left upper and lower extremities was noted. There was a long history of rheumatic heart disease, with fibrillation; this had been treated by digitalization and diuretics for five years. Chronic ascites was noted to have increased during the week prior to admission.

Physical Examination.—The patient was disoriented and confused. There was a complete flaccid hemiplegia on the left side, with ipsilateral increased deep tendon reflexes and Babinski's plantar reflex. A supranuclear facial weakness was noted on the left. In addition, a left homonymous hemianopsia and hemisensory disturbances were found. The heart was enlarged, with distant sounds and a grossly irregular pulse rate. The abdomen was markedly distended by ascitic fluid. Blood pressure measured 116/80 mm. Hg, and pulse rate was 60 per minute and irregular.

Laboratory Data.—The blood cell count and findings on urinalysis were within normal limits. An electrocardiogram showed auricular fibrillation, with slow ventricular rate, right axis deviation, and low-voltage QRS complexes. Angiography demonstrated nonfilling of the middle cerebral group of vessels (fig. 3A).

Course.—The patient was immediately administered 100,000 units of fibrinolysin in 50 cc. of isotonic sodium chloride solution, intravenously. On the six successive days she received the same amount of enzyme in 200 cc. of solution, by infusion, over a one-hour period. The temperature was elevated to 101 F (38.3 C), with daily spikes ranging from 103 to 105 F (39.4 to 40.5 C). There were a few hypotensive phenomena, with occasional blood pressure readings of 100/60 mm. Hg. During the last five days of treatment, the patient could occasionally extend the left lower extremity at the knee. On the eighth day, a repeat carotid arteriogram revealed good filling of the middle cerebral group (fig. 3 *B*).

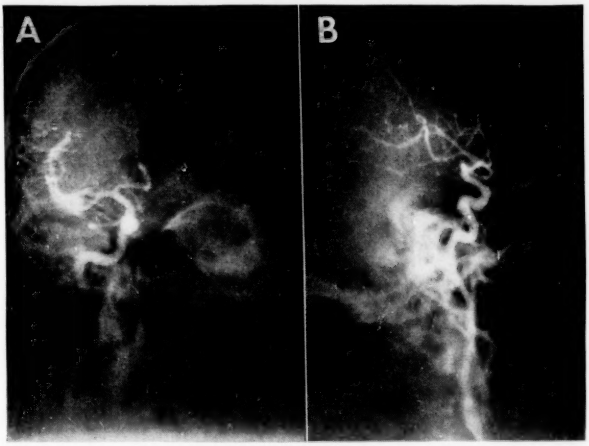

Fig. 2 (case 2).—A, anteroposterior arteriogram, showing occlusion of the anterior cerebral artery immediately beyond the frontopolar branch and nonvisualization of the pericallosal and callosomarginal vessels. *B*, lateral arteriogram, with only the main trunk and frontopolar and prefrontal branches of the anterior cerebral artery seen. Vessel is seen to truncate abruptly at point of occlusion immediately beyond frontopolar origin.

Comment

The primary problem in this group of cases was the uncertain nature of the occluding lesion. In the third patient, in whom the most gratifying results were obtained, it is assumed that the source of obstruction was an embolus originating in the fibrillat-

ing auricle. She was treated, after study, within six hours of the appearance of symptoms. There was some speculation while this patient was under treatment whether the composition of the embolus might be older than the short clinical course suggested. It is believed, however, that the lodging embolus actually was the released fragment of a fresh thrombus. It is this type of fresh clot that is probably most susceptible to the lytic agent. The arteriograms suggest that, in this case, a restitution of the sylvian artery circulation was accomplished. The first patient treated was not seen until a week after the onset of symptoms. It is not believed that a thrombus of this age is a satisfactory substrate for the digestive action of the enzyme, although some lytic action was demonstrated in this case. The possibilities of a subintimal dissection of the wall underneath an atherosclerotic plaque or a progressive sclerosis are further situations in which it is not reasonable to expect drug action. It is possible that one of these factors accounted for the failure in the second patient. In the large group of cases, however, where a fresh thrombus is the final source of occlusion, it is believed that the drug may be effective if administered promptly.

Studies of the blood levels of the enzyme were conducted on all three patients. The use of the drug has been implemented on an empirical basis. It is not certain what constitutes a satisfactory therapeutic dose or course of treatment. We do not know how soon the thrombus may be expected to dissolve. The possibility of greater advantage to be obtained from intracarotid administration has been considered. Some preliminary work along this line was carried out on the first patient. Further studies are being conducted.

There was observed a consistent pyrogenic effect of the drug, as well as some mild hypotensive episodes in two patients. These side-actions were not deleterious in these cases and did not require treatment. We have encountered no evident complications of fibrinolysin administration.

It is of clinical interest that the patient with anterior cerebral artery occlusion developed a complete hemiplegia, with transient sensory deficits. In characteristic fashion, the lower limb was involved first, with associated proximal upper limb weakness that spared the hand. The complete paralysis that followed, however, showed signs of improvement in the lower limb alone. This provocative correlation raises anew the question of how extensively the motor cortex may be represented along the medial surface of the hemisphere. In addition, it is further evident that our clinical localization of the site of thrombosis may be very subject to error.

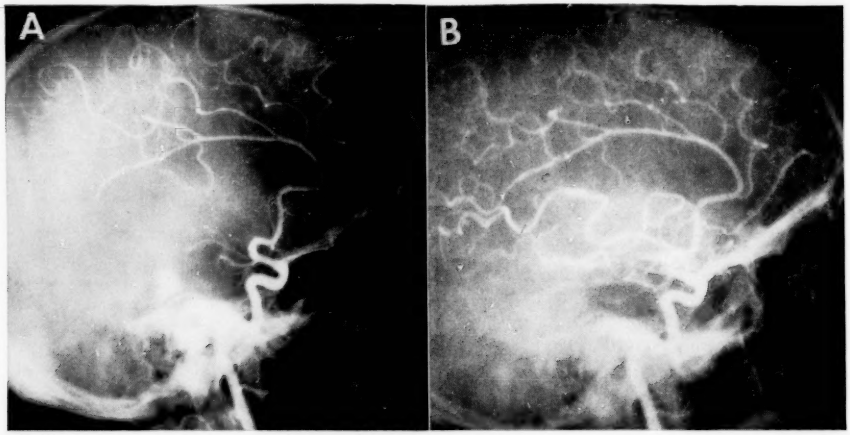

Fig. 3 (case 3).—*A*, arteriogram showing occlusion of middle cerebral artery at origin from carotid. Only anterior cerebral, posterior communicating, anterior choroidal, and posterior cerebral branches of carotid are seen. *B*, good visualization of sylvian artery group, except for ascending frontal branches, seven days after treatment.

There were no untoward reactions to angiography in this group of patients. Although we are not enthusiastic about the repeated performance of arteriography in patients with cerebrovascular disease, we have not observed complications in this group or in another previously reported.[1d] There is, unfortunately, no alternative to arteriography before and after treatment. Clinical improvement is a poor indicator of efficacy, for this usually occurs to some degree in most cases of cerebral thrombosis.

Summary

In a preliminary study, three patients with occlusive carotid or cerebral vascular disease were treated with fibrinolysin. Arteriography demonstrated the site of obstruction in all three cases. Restitution of the middle cerebral artery circulation was observed in one patient. In a second, partial clearing of an occluded carotid lumen was observed. The other patient showed no alteration of his anterior cerebral artery occlusion. We are impressed with the possible advantageous action of fibrinolysin. It is believed that its prompt administration in cases of cerebral thrombosis or embolism may prove beneficial. It is not expected to benefit patients with progressive atherosclerotic occlusion in whom an actual thrombus does not occlude the lumen. Its specific usefulness in treatment of embolism has been suggested by the results obtained in one patient. Further studies are being carried out.

916 Park Ave. (Dr. Sussman).

The fibrinolysin used in this study was supplied as Actase by the Ortho Research Foundation, Raritan, N. J.

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CHRONIC CONSTRICTIVE PERICARDITIS.—In the 21 years from 1935 through 1955, 72 patients have undergone operation for constrictive pericarditis at the clinic. Follow up data were available for periods varying from three months to 17 years from examination at the clinic or from follow up letters. There were 49 males and 23 females in this series, and the majority were from ten to 39 years old. Many disease entities have been considered precursors of chronic constrictive pericarditis. The great majority of these cases, however, were not associated with any condition which might be blamed etiologically. Only 19 of the 72 patients gave a history of any previous infection or incident which conceivably might have been related to the development of constrictive pericarditis. Eleven afforded microscopic evidence of granulomatous pericariditis compatible with tuberculosis. In only six of the 11, however, could tubercle bacilli be isolated by culture. In 59 instances the pathologist diagnosed chronic nonspecific pericarditis, and in two additional cases both acute and chronic pericarditis of a nonspecific variety were present; but no single factor or group of them was found consistently to account for the onset of constrictive pericarditis.—J. C. Cooley, M.D.; O. T. Clagett, M.D.; and J. W. Kirklin, M.D., Surgical Aspects of Chronic Constrictive Pericarditis, *Annals of Surgery*, April, 1958.

Summary

A pilot study of the effects of intravenously given fibrinolysin (plasmin) has been carried out in 52 patients with various forms of thromboembolic disease. Toxicity, fibrinolytic activity achieved in the plasma, and therapeutic results were carefully evaluated.

In the doses used, toxicity of the agent appears limited to pyrogenicity, which was encountered in 49.2% of the patients. The mechanism of this response has not been defined. Two instances of delayed allergic skin reactions were noted. No embolic events have followed fibrinolysin infusion. Serial study of coagulation factors after infusion of fibrinolysin showed no clinically significant derangement of the coagulative process. No hemorrhagic phenomena were encountered in any patient, including 29 who were simultaneously receiving anticoagulant drugs.

Fibrinolytic activity of the plasma was consistently enhanced by fibrinolysin infusion. The intensity and duration of such activity paralleled total fibrinolysin dosage.

While the therapeutic results observed after infusion of fibrinolysin in several varieties of thromboembolic disease were encouraging, firm conclusions regarding its therapeutic value cannot be drawn from this pilot study and must await completion of large-scale controlled studies. However, the observations reported here do justify a cautious optimism that fibrinolysin may prove a safe and effective agent for achieving acute lysis of intravascular clot.

District of Columbia General Hospital, 19th and E streets S. E. (3).

The fibrinolysin used in this study was supplied as Actase by the Ortho Research Foundation, Raritan, N. J.

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SCHOOL HEALTH.—One of the first things that will bring about a mutual understanding between school health and public health is a policy on communicable disease control. A complete and satisfactory agreement can be made with regard to local control of communicable diseases in a joint meeting with the school health committee of the County Medical Society, local health officers and the director of school health. . . . In planning a health education program, public schools and public health agencies should join with other agencies and make it a community project. A community health council organized by all official and non-official agencies in the community may serve as a clearing-house for all community health education program planning. Newer methods of health education can be developed and put into action when the community agencies work together.—A. E. Hill, M.D., M.P.H., Correlation Between School Health and Public Health, *The Journal of School Health*, May, 1958.

THROMBOLYSIS WITH FIBRINOLYSIN IN CEREBRAL ARTERIAL OCCLUSION

Bernard J. Sussman, M.D.
and
Thomas S. P. Fitch, M.D., Plainfield, N. J.

Three patients with hemiplegia were treated by the slow intravenous infusion of fibrinolysin. The site of occlusion of the cerebral vessels was located in each case by arteriography. In one case the angiograms clearly showed nonfilling of the middle cerebral group of arteries before treatment, while on the eighth day after beginning treatment good filling of the middle cerebral vessels was obtained. This patient showed the most favorable results. The history of rheumatic heart disease and the fact that treatment was commenced within six hours after the onset of symptoms suggest that the lesion was caused by an embolus originating in the fibrillating left atrium and that the embolus was a fresh thrombus most susceptible to the lytic agent. No detrimental effects that could be ascribed either to the diagnostic angiography or to the administration of fibrinolysin were observed in these patients.

The most promising therapy for thrombotic occlusion of any vessel supplying the brain will probably be immediate solution of the clot by a parenterally administered agent. A surgically directed approach to the problem may be frustrated by the increasingly apparent complexities of vascular thrombosis. The appearance of symptoms may depend on complicated relationships between anastomotic channels. There is increasing evidence to make us speculate that a hemiplegia resulting from an apparent angiographically demonstrated thrombosis of the carotid artery, or of its cerebral branches, may actually result from the final thrombotic closure or stenosis of a vital collateral vessel elsewhere that is compensating for a long-standing obliterated proximal channel. Although transient neurological deficits may be related to alterations of the general systemic blood pressure, on which the stability of the collateral circulation depends, the more persistent and complete deficits are more likely the result of a final strategic thrombosis or other form of occlusion. Whatever might be done by the surgeon electively for lesser symptoms when the site of thrombosis or stenosis is demonstrable, in the presence of a severe neurological deficit, only the immediate elimination of the thrombus is likely to be of benefit. It is not believed practical that this can be accomplished surgically in the majority of instances.

There have been many reports in recent years of angiographically proved cases of carotid or major cerebral artery thrombosis.[1] Several workers have undertaken a surgical approach to the problem. Strully and associates[2] performed an incomplete thromboendarterectomy in 1953 in a patient with signs of aphasia and visual disturbance. They speculated that, under more favorable circumstances, the procedure might be effective. We have recently observed such a satisfactory complete removal of the thrombus within 24 hours of the appearance of hemiplegia and aphasia. Although vigorous flow was at least temporarily reestablished, the patient obtained no improvement. We have witnessed marked improvement after carotid thromboendarterectomy in a case of partial aphasia and hemiparesis; however, we cannot be certain that the surgery was responsible. Arnstein[3] is more enthusiastic about this procedure, although only 2 of his 10 patients would appear to have been radically improved after total deficit. Eastcott and associates,[4] Lin and co-workers,[5] Denman and associates,[6] and others have attempted to remedy either minor or recurrent episodes of neurological deficit by various other techniques, generally consisting of a vascular bridging graft or resection of the diseased arterial carotid segment. Although some improvement has been obtained under these circumstances, there has not yet been reported a patient with hemiplegia or global deficit who has made dramatic recovery after one of these procedures. Some lesser degree of recovery is to be expected without intervention. In this respect, Jackson[7] has recently demonstrated how, in two cases of improvement, the supposedly restored channel was proved to be obliterated at reexploration or angiography. In addition, surgery may actually interfere with the collateral if, unwittingly, the external carotid artery is kept from its function of supplying flow via the ophthalmic artery to the carotid, as shown by Vaernet.[8]

It is our feeling that the results of these procedures are not very encouraging, particularly under the circumstances of global deficit. With minor deficits or recurrent episodes, it is very likely

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that, in conjunction with anticoagulants, they offer some therapeutic and prophylactic promise. In the severe cases, the principal handicap inherent in this technique is the poorly tolerated delay between the appearance of symptoms and the removal of the thrombus. As demonstrated by Denny-Brown and Meyer,[9] this critical period must be very short before the changes in the damaged area of the brain become irreversible. This time is ordinarily consumed in the obligatory delay required for consultation between family physician and specialist, transportation, diagnostic angiography, and preparation for surgery. What has been needed is an agent, known to be effective in reversing thrombosis, which can be administered immediately on the appearance of symptoms by the first physician to arrive on the scene. Needless to say, the applicability of such a drug in the smaller vessel thromboses is enormous. It is hoped that in this study, in which the enzyme fibrinolysin has been used, there may be some promise of such an agent.

Fibrinolysin (plasmin)[10] is a naturally occurring proteolytic enzyme of plasma. Purified human plasminogen or profibrinolysin, its precursor, may be spontaneously activated in vivo to fibrinolysin or in vitro by urokinase (an enzyme obtained from urine). The effect of fibrinolysin, as demonstrated by many workers,[11] is the dissolution of vascular thrombi. This drug has been used clinically in the three patients reported here. Particular attention is invited to the third case.

Report of Cases

Case 1.—A 75-year-old woman, right-handed, was admitted to the hospital on Sept. 6, 1957, because of the abrupt appearance of hemiplegia of the right side and inability to speak. She was known to have hypertension of many years' duration and had required recent treatment for dyspnea and cystitis.

Physical Examination.—The patient aroused easily but could not speak and did not comprehend. A complete spastic hemiplegia on the right side was evident, with increased deep tendon reflexes and ipsilateral Babinski's signs. There was a moderate supranuclear facial weakness on the right. A resting alternating tremor of the left hand and forearm was observed. The carotid pulsations on the left varied on repeated examinations. Cardiac enlargement and a systolic apical murmur were noted. The blood pressure was 180/90 mm. Hg.

Laboratory Data.—The blood cell count was normal. Urinalysis revealed 1+ albumin, 6-10 white blood cells, 80-120 red blood cells, and bacteria. A left carotid arteriogram performed on Sept. 12, 1957, demonstrated nonfilling of the internal carotid artery beyond the bifurcation of the common carotid (fig. 1*A*).

Course.—On the same day, 50,000 units of fibrinolysin was given intravenously in 300 cc. of isotonic sodium chloride solution over a three-hour period. Simultaneously, 25,000 units in 100 cc. was given after one hour, over a 15-minute period, into the left carotid artery. This was repeated on three of the next four days. One injection of 200 mg. of heparin was administered on the day no fibrinolysin was given. A second left carotid arteriogram taken on Sept. 16, 1957, showed an incomplete 2-cm. column of dye in the proximal internal carotid (fig. 1*B*). Accordingly, 75,000 units of fibrinolysin was given daily, intravenously, in 500 cc. of isotonic sodium chloride solution over a two-hour period for the following six days. On Sept. 24, 1957, another

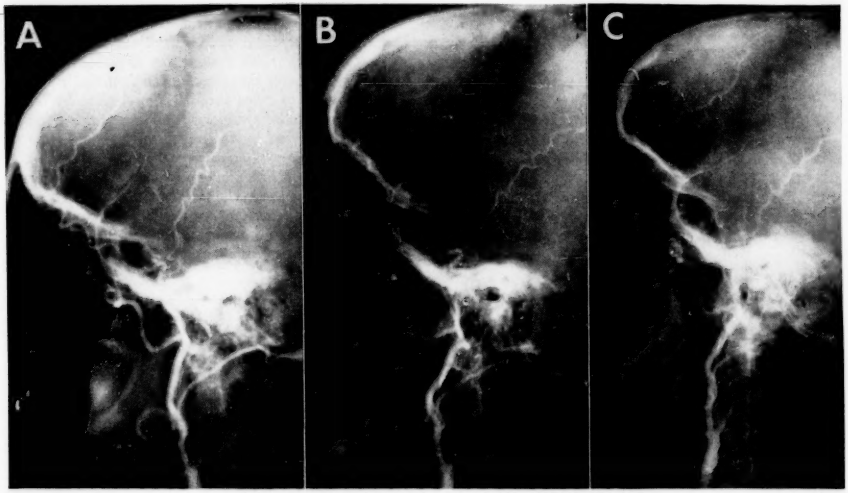

Fig. 1 (case 1).—*A*, arteriogram showing thrombosis of internal carotid artery at bifurcation of common carotid. *B*, evidence of partial clearing of internal carotid after six days of therapy. *C*, slight further clearing after six additional days of therapy.

left carotid arteriogram showed slight further change (fig. 1C). No hypotensive effects of the drug were observed in this patient. There was some elevation of temperature, which ranged between 101 and 102 F (38.3 and 38.7 C), but this may have been due to chronic cystitis. The patient showed no improvement of her hemiplegia or aphasia. She appeared more alert, however, and was able to take oral feedings better after the course of treatment.

CASE 2.—A 52-year-old right-handed man was admitted to the hospital on Sept. 28, 1957, because of progressive hemiparesis of the left side. About one hour prior to admission, he noted weakness of the left lower extremity, which rapidly became complete. He had been in good health prior to this illness.

Physical Examination.—The patient was alert but somewhat facetious. There was a complete, slightly spastic paralysis of the left lower extremity. The left upper extremity was weak and much more spastic than the lower, with most involvement proximally. The deep tendon reflexes were hyperactive on the left. A Babinski's plantar reflex was obtained on the left. Findings in the general physical examination were within normal limits. The blood pressure was 130/80 mm. Hg, and the pulse rate was 90 per minute and regular.

Laboratory Data.—Blood cell count and findings on urinalysis were normal. A right carotid arteriogram performed six hours after admission demonstrated occlusion of the anterior cerebral artery at the point of bifurcation into the pericallosal and callosomarginal vessels (fig. 2).

Course.—Immediately after angiography, the patient received, intravenously, 100,000 units of fibrinolysin in 50 cc. of isotonic sodium chloride solution over a two-minute period. On each of the following five days, an infusion of 100,000 units was given in 500 cc. over a two-hour period. On Oct. 3, 1957, angiography failed to reveal any further filling of the anterior cerebral artery. During this period, a progression to a complete hemiplegia of the left side was noted. This was associated with a tendency to ignore the paralyzed limb and a mild hypalgesia over the left side of the body, as well as defective proprioception. These sensory findings gradually disappeared as the patient became aware of his deficit. In addition, there was noted a disappearance of the spasticity of the left upper extremity and an occasional demonstration of ability to extend the left lower extremity when supported by the examiner. During the course of therapy, a sustained temperature elevation of 102 to 103 F (38.7 to 39.4 C) was observed. This reverted to normal after cessation of the enzyme administration. A solitary hypotensive episode with a blood pressure reading of 90/40 mm. Hg was seen on the fifth day of treatment.

CASE 3.—The patient, a 50-year-old right-handed woman, was admitted to the hospital on Oct. 22, 1957, after falling from bed on attempting to arise that morning. A paralysis of her left upper and lower extremities was noted. There was a long history of rheumatic heart disease, with fibrillation; this had been treated by digitalization and diuretics for five years. Chronic ascites was noted to have increased during the week prior to admission.

Physical Examination.—The patient was disoriented and confused. There was a complete flaccid hemiplegia on the left side, with ipsilateral increased deep tendon reflexes and Babinski's plantar reflex. A supranuclear facial weakness was noted on the left. In addition, a left homonymous hemianopsia and hemisensory disturbances were found. The heart was enlarged, with distant sounds and a grossly irregular pulse rate. The abdomen was markedly distended by ascitic fluid. Blood pressure measured 116/80 mm. Hg, and pulse rate was 60 per minute and irregular.

Laboratory Data.—The blood cell count and findings on urinalysis were within normal limits. An electrocardiogram showed auricular fibrillation, with slow ventricular rate, right axis deviation, and low-voltage QRS complexes. Angiography demonstrated nonfilling of the middle cerebral group of vessels (fig. 3A).

Course.—The patient was immediately administered 100,000 units of fibrinolysin in 50 cc. of isotonic sodium chloride solution, intravenously. On the six successive days she received the same amount of enzyme in 200 cc. of solution, by infusion, over a one-hour period. The temperature was elevated to 101 F (38.3 C), with daily spikes ranging from 103 to 105 F (39.4 to 40.5 C). There were a few hypotensive phenomena, with occasional blood pressure readings of 100/60 mm. Hg. During the last five days of treatment, the patient could occasionally extend the left lower extremity at the knee. On the eighth day, a repeat carotid arteriogram revealed good filling of the middle cerebral group (fig. 3 *B*).

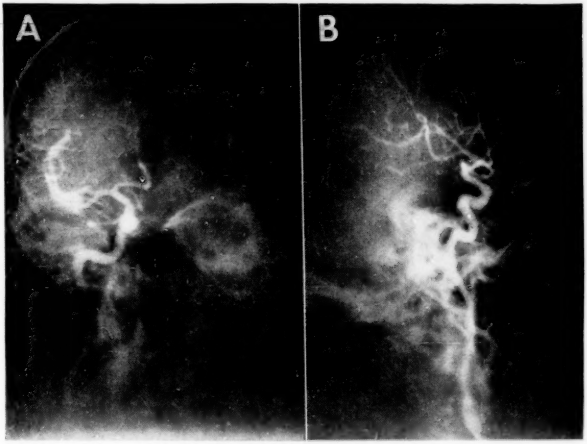

Fig. 2 (case 2).—*A*, anteroposterior arteriogram, showing occlusion of the anterior cerebral artery immediately beyond the frontopolar branch and nonvisualization of the pericallosal and callosomarginal vessels. *B*, lateral arteriogram, with only the main trunk and frontopolar and prefrontal branches of the anterior cerebral artery seen. Vessel is seen to truncate abruptly at point of occlusion immediately beyond frontopolar origin.

Comment

The primary problem in this group of cases was the uncertain nature of the occluding lesion. In the third patient, in whom the most gratifying results were obtained, it is assumed that the source of obstruction was an embolus originating in the fibrillat-

ing auricle. She was treated, after study, within six hours of the appearance of symptoms. There was some speculation while this patient was under treatment whether the composition of the embolus might be older than the short clinical course suggested. It is believed, however, that the lodging embolus actually was the released fragment of a fresh thrombus. It is this type of fresh clot that is probably most susceptible to the lytic agent. The arteriograms suggest that, in this case, a restitution of the sylvian artery circulation was accomplished. The first patient treated was not seen until a week after the onset of symptoms. It is not believed that a thrombus of this age is a satisfactory substrate for the digestive action of the enzyme, although some lytic action was demonstrated in this case. The possibilities of a subintimal dissection of the wall underneath an atherosclerotic plaque or a progressive sclerosis are further situations in which it is not reasonable to expect drug action. It is possible that one of these factors accounted for the failure in the second patient. In the large group of cases, however, where a fresh thrombus is the final source of occlusion, it is believed that the drug may be effective if administered promptly.

Studies of the blood levels of the enzyme were conducted on all three patients. The use of the drug has been implemented on an empirical basis. It is not certain what constitutes a satisfactory therapeutic dose or course of treatment. We do not know how soon the thrombus may be expected to dissolve. The possibility of greater advantage to be obtained from intracarotid administration has been considered. Some preliminary work along this line was carried out on the first patient. Further studies are being conducted.

There was observed a consistent pyrogenic effect of the drug, as well as some mild hypotensive episodes in two patients. These side-actions were not deleterious in these cases and did not require treatment. We have encountered no evident complications of fibrinolysin administration.

It is of clinical interest that the patient with anterior cerebral artery occlusion developed a complete hemiplegia, with transient sensory deficits. In characteristic fashion, the lower limb was involved first, with associated proximal upper limb weakness that spared the hand. The complete paralysis that followed, however, showed signs of improvement in the lower limb alone. This provocative correlation raises anew the question of how extensively the motor cortex may be represented along the medial surface of the hemisphere. In addition, it is further evident that our clinical localization of the site of thrombosis may be very subject to error.

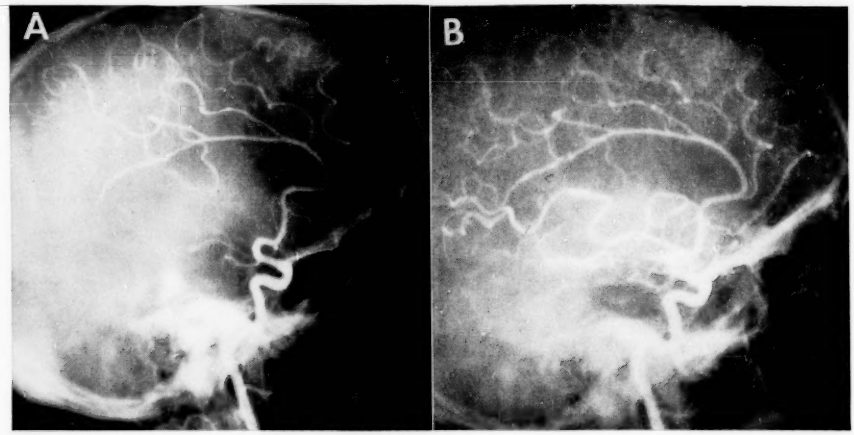

Fig. 3 (case 3).—*A*, arteriogram showing occlusion of middle cerebral artery at origin from carotid. Only anterior cerebral, posterior communicating, anterior choroidal, and posterior cerebral branches of carotid are seen. *B*, good visualization of sylvian artery group, except for ascending frontal branches, seven days after treatment.

There were no untoward reactions to angiography in this group of patients. Although we are not enthusiastic about the repeated performance of arteriography in patients with cerebrovascular disease, we have not observed complications in this group or in another previously reported.[14] There is, unfortunately, no alternative to arteriography before and after treatment. Clinical improvement is a poor indicator of efficacy, for this usually occurs to some degree in most cases of cerebral thrombosis.

Summary

In a preliminary study, three patients with occlusive carotid or cerebral vascular disease were treated with fibrinolysin. Arteriography demonstrated the site of obstruction in all three cases. Restitution of the middle cerebral artery circulation was observed in one patient. In a second, partial clearing of an occluded carotid lumen was observed. The other patient showed no alteration of his anterior cerebral artery occlusion. We are impressed with the possible advantageous action of fibrinolysin. It is believed that its prompt administration in cases of cerebral thrombosis or embolism may prove beneficial. It is not expected to benefit patients with progressive atherosclerotic occlusion in whom an actual thrombus does not occlude the lumen. Its specific usefulness in treatment of embolism has been suggested by the results obtained in one patient. Further studies are being carried out.

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The fibrinolysin used in this study was supplied as Actase by the Ortho Research Foundation, Raritan, N. J.

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CHRONIC CONSTRICTIVE PERICARDITIS.—In the 21 years from 1935 through 1955, 72 patients have undergone operation for constrictive pericarditis at the clinic. Follow up data were available for periods varying from three months to 17 years from examination at the clinic or from follow up letters. There were 49 males and 23 females in this series, and the majority were from ten to 39 years old. Many disease entities have been considered precursors of chronic constrictive pericarditis. The great majority of these cases, however, were not associated with any condition which might be blamed etiologically. Only 19 of the 72 patients gave a history of any previous infection or incident which conceivably might have been related to the development of constrictive pericarditis. Eleven afforded microscopic evidence of granulomatous pericariditis compatible with tuberculosis. In only six of the 11, however, could tubercle bacilli be isolated by culture. In 59 instances the pathologist diagnosed chronic nonspecific pericarditis, and in two additional cases both acute and chronic pericarditis of a nonspecific variety were present; but no single factor or group of them was found consistently to account for the onset of constrictive pericarditis.—J. C. Cooley, M.D.; O. T. Clagett, M.D.; and J. W. Kirklin, M.D., Surgical Aspects of Chronic Constrictive Pericarditis, *Annals of Surgery,* April, 1958.

ADJUVANT USE OF CHEMOTHERAPY IN THE SURGICAL TREATMENT OF CANCER

PLAN OF COOPERATIVE STUDY

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A plan is described for the cooperation of 48 departments of surgery under the auspices of the National Cancer Institute in a study of the effectiveness of chemotherapy as an adjuvant to the surgical treatment of cancer. It has three aims: to improve the prognosis of the patient with cancer, to determine whether certain chemical agents are curative, and to develop workable techniques for therapeutic trials. Two investigations specifically planned relate to the use of Thio-TEPA (triethylenethiophosphoramide) in resectable gastric carcinoma and of nitrogen mustard in resectable pulmonary carcinoma. The results of animal research encourage such work, since small tumors have been found more susceptible than larger ones to regression, and the probability of metastasis is less when the number of neoplastic cells in the primary tumor is small. The plan includes the use of standard criteria of diagnosis, treatment, and measurement of effect; the pooling of data from all collaborating institutions; and the participation of statisticians in designing the study and evaluating the results.

This report presents some of the background and the study plan of a large national endeavor in clinical research on cancer that has been developed under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute. The study is known as the Adjuvant Use of Chemotherapy in the Surgical Treatment of Cancer, and its major purpose is to assess the effect of known anticancer chemical agents when administered in conjunction with definitive treatment of cancer at a stage when the neoplasm may be clinically curable. The aims of the study are threefold: (1) to establish whether this additional measure will yield improvement in the end-results, (2) to ascertain whether some of the presently available anticancer agents which have had only a palliative effect against established neoplasms may have a curative effect in earlier stages of cancer, and (3) to develop methods and techniques for clinical therapeutic trials in cancer.

The participation of 48 departments of surgery in these studies and the approval and support of this research by the National Advisory Cancer Council are the results of gradual changes in concepts regarding cancer. These concepts have led to the realization of the limitations of surgical and radiologic treatment of cancer that attempts to circumscribe and to remove the neoplasm and to the realization of the possibility of discovering effective chemical agents against cancer.

The First Aim

The first aim of these clinical studies is directly therapeutic: to improve the prognosis of the patient with cancer. It is possible to record steady albeit slow improvement in the end-results of the treatment of cancer in the United States.[1] The basic problem of the excisional approach to cancer, however, is that a majority of patients in whom the local disease has been eradicated die from the distant spread of cancer cells through lymphatics, vascular channels, and body cavities.

Research work on animals has demonstrated that very early spread of tumor cells can occur to sites distant from implanted tumors but that a relatively small proportion of such cells gives rise to eventual metastatic growth.[2] Although the transplantation of leukemia and some sarcomas in mice can be accomplished by inoculation with a single neoplastic cell,[3] successful transplantation of most tumors requires rather large numbers of tumor cells.[4]

It seems likely that similar factors may be involved in man during the transplantation process of metastasis. Smith and his co-workers [5] recently have reported on the recovery of tumor cells from the washings of operative wounds for cancer. The most interesting finding was that almost half of the patients in whom such tumor cells were identified did not develop local recurrence.

In chemotherapeutic research on animals with transplanted neoplasms, it has been the practice to use tumors after they have become well established and are actively growing in the new host. It is known that, during the earlier stages of tumor growth, conditions between the tumor and the host are different from conditions at later stages and that small tumors appear to be more

From the National Cancer Institute (Dr. Shimkin) and Roswell Park Memorial Institute (Dr. Moore).

susceptible to regression than larger ones. The interrelationships between tumor, host, and drug recently have been reviewed by Goldin.[6]

Recent experimental work further substantiating that earlier, unestablished tumor foci are more susceptible to destruction than established, larger tumors has been published by Goldie and associates,[7] who used radioisotopic materials, and by Cruz and associates,[8] Kramer and associates,[9] and by Lapis and Németh,[10] who used alkylating chemicals. The intricate mechanisms that may be involved are suggested by the finding of Kramer and associates[9] that Thio-TEPA (triethylenethiophosphoramide) is more effective in preventing pulmonary growth of melanoma S-91 in mice when it is given one or two days after tumor cell inoculation than when it is given immediately after the intravenous transplantation. Shapiro and Fugmann[11] reported an experiment in mice bearing carcinoma 755, in which four groups of animals were treated as follows: (1) with no surgery or chemotherapy, (2) with chemotherapy only, (3) with surgical excision only, and (4) with subtotal surgical excision and chemotherapy. In this particular system there were no survivors among the first three groups, whereas half of the mice in the fourth group became free of tumor.

In most of the studies mentioned above, the investigators used a tumor which was sensitive to the particular chemical agent. Furthermore, all of the tumors were transplants, and thus some host reactions can be assumed. When relatively unresponsive tumor-agent combinations are used, the chemotherapeutic action upon even unestablished tumor cells may be negligible.

If toxic chemotherapeutic compounds do not destroy the cancer cells and do decrease the host's resistance, an adverse effect on the host may occur. Many investigators have noted that cortisone reduces host resistance, with resultant acceleration of tumor implantation and growth. Kondo and Tsukui[12] demonstrated this phenomenon by treating animals with Nitromin (2,2′-dichloro-N-methyldiethylamine N-oxide hydrochloride) before inoculation of tumor cells. Personal experience suggests that enhanced growth of advanced neoplasms in patients may take place if an ineffective toxic anticancer agent is used.

There have been several clinical studies in which chemical or radioisotopic agents were used in conjunction with the surgical treatment of cancer. These investigations are distinctly different in approach from the earlier combinations of radiation and surgery, where essentially an enhanced local or regional effect was the intent.

Low-Beer and Bell[13] administered radiophosphorus in conjunction with radical mastectomy for breast cancer; the authors previously found some differential absorption of radiophosphorus by breast tumors. Cole and his colleagues[14] deserve credit for initiating and developing interest in the United States in the use of nitrogen mustard and Thio-TEPA at the time of surgical resection of gastrointestinal neoplasms. It is reported from Japan[15] that Nitromin is being used after surgical treatment of a wide variety of neoplasms. In Germany and Austria[16] both Nitromin and E-39 [2,5-bis-(ethylenimino)-3,6-dipropoxy-*p*-benzoquinone] are being explored as adjuvants to surgery. None of these studies has as yet provided definite answers regarding the effects of adjuvant therapy.

The Second Aim

The second aim of the studies is a corollary of the first: to determine whether certain chemical agents are curative in human cancer. The modern era of research in the chemotherapy of cancer began under the cloak of wartime secrecy, with the discovery of the antineoplastic activity of nitrogen mustard by Gilman and Philips. By 1948 there had appeared the work on antifolic compounds by SubbaRow and their clinical application by Farber and on urethane and the alkylating agents by Haddow and his group. The work in this exciting field, still in its infancy, has been summarized recently by Farber and associates.[17] Except for the effect of antifolic compounds and 6-mercaptopurine in childhood leukemia, no significant prolongation of life can be demonstrated with the use of chemical agents in advanced neoplastic disease in man. Yet some of these compounds are sufficiently active to cure certain established transplantable neoplasms in rodents. It would certainly be useful and encouraging to the further development of this line of research if it could be demonstrated that chemotherapeutic agents for cancer already available have curative activity under more favorable circumstances than those presented by patients with neoplasms no longer amenable to any other therapeutic approach.

This possibility can be explored in human beings only in the form of adjuvant therapy for two reasons: 1. Moral and ethical considerations preclude the use of chemotherapy as the sole form of treatment when curative techniques are available. 2. Early tumors comparable to those utilized in animal experiments are diagnosed but rarely in man. Therefore, surgical excision of the gross tumor followed by chemotherapy for the residual cells appears to be the appropriate clinical experimental situation.

The Third Aim

The third aim of the cooperative group effort is to develop workable methods and techniques for therapeutic trials in cancer. Research in cancer has been retarded by lack of standard definitions of diagnosis, treatment, and response, with the result that series of clinical chemotherapeutic trials reported by different investigators are almost never directly comparable. Uniform criteria for admission of patients to the study, of the treatment

schedule, and of subsequent observations are essential to a meaningful pooling or comparison of data. Pooling from several medical centers is desirable in order that an adequate number of patients for analysis can be gathered within a reasonable period of time.

As stated previously, these clinical studies are predicated upon the hypothesis that chemical materials which have some effectiveness against advanced human neoplasms may have greater effect when directed against much smaller, earlier distant deposits of the tumors, microscopic amounts of residual tumors, and unestablished tumor cells. It is evident, therefore, that the only reliable end-point of the investigations is the determination of survival in a sufficient number of patients treated with a chemical agent, as compared with the survival in an entirely comparable group of patients treated in an identical fashion but not receiving the adjuvant material.

Such comparability is possible only by the use of strict randomization procedures, through which patients enter the study group and the control group by laws of chance rather than by selection. A great advantage of this method is that a minimal number of patients is exposed to potentially dangerous procedures or agents in providing a reliable evaluation in the shortest possible time.

It is hoped that these studies will stimulate the initiation of similar strictly controlled group studies on the effectiveness of other types of treatment for cancer. For example, the addition of thousands of cases to the individual series already available on radical mastectomy and on simple mastectomy plus radiation would not clarify the essential issues. What is needed is a therapeutic trial in which such a comparison would be carried out with the patients entering each group on a randomized basis.

The Cooperative Studies

The present cooperative studies on the adjuvant use of chemotherapy in the surgical treatment of cancer were organized in November, 1956, under the leadership of the Clinical Studies Panel of the Cancer Chemotherapy National Service Center. The studies could not have been developed without the interest and support of Dr. I. S. Ravdin, chairman of the Clinical Studies Panel, and of Dr. K. M. Endicott, chief of the Chemotherapy Center.

The panel decided that the first studies should include neoplasms with a poor prognosis which were known to be affected by the chemotherapeutic agent employed and others which were considered insensitive to such chemicals. This decision led to the selection of two investigations, one on pulmonary carcinoma, with nitrogen mustard as the chemical adjuvant, and the other on gastric carcinoma, with Thio-TEPA for adjuvant chemotherapy.

The study plan, or protocol, for gastric carcinoma is representative of the experimental design of such studies. It was developed by a group of clinical investigators with the participation of statisticians. Since Thio-TEPA, the chemical proposed for trial, is a powerful hematopoietic depressant, a preliminary study was carried out by a number of participating clinicians to ascertain that the recommended dose schedule did not produce serious additional morbidity in surgically treated patients.

The following principles were agreed upon: (1) pooling of data from all institutions in order to accumulate rapidly the necessary number of patients; (2) standard criteria of diagnosis, treatment, and measurement of effect; (3) statistical design of the study, with randomized assignment of patients to the groups to be compared; and (4) statistical analysis and collaborative reporting of the results.

The protocol includes detailed definitions and instructions for the determination of patient eligibility, such as exclusion of patients with gastric lymphosarcoma and with metastatic lesions. It indicates the minimal clinical and laboratory procedures that must be performed preoperatively and postoperatively.

The exact surgical procedure of gastrectomy is left to the discretion of the surgeon, but unusual techniques are excluded. The patients are classified into three therapeutic categories: (1) total gastrectomy with curative intent, (2) partial gastrectomy with curative intent, and (3) total or partial gastrectomy with palliative intent. Patients with nonresectable lesions are excluded from the formal study.

Randomization of patients into the group receiving adjuvant chemotherapy and those not receiving chemotherapy is achieved by a closed envelope technique. The surgeon is not informed of the assignment of the patient until after the excisional procedure has been completed so as not to introduce any possible influence upon the kind or extent of the operation. It is only before the closing of the abdomen that an envelope prepared by the central statistical unit is opened and the assignment instructions therein are followed.

The schedule of administering Thio-TEPA to the patients falling into the chemotherapy group is as follows: Upon completion of the operation, 0.2 mg. per kilogram of body weight is injected into a portal vein and 0.2 mg. per kilogram into the peritoneal cavity. On the first and second postoperative days, 0.2 mg. per kilogram is injected intravenously, for a total dose of 0.8 mg. per kilogram of body weight during a period of three days. All Thio-TEPA is from one lot, prepared for intravenous use.

Follow-up examinations are designed to obtain information on the effect of the chemotherapeutic agent upon the hematopoietic system and on the subsequent course of the patient. Survival rather than recurrence or metastasis is adopted as the criterion of effect.

The flow-sheet of the study of gastric carcinoma is given in the figure.

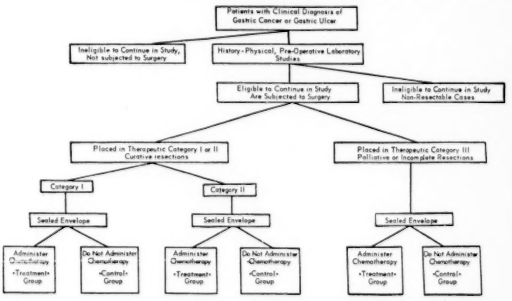
All patients entering the study are reported to a central statistical unit as soon as the randomized assignment is made at the operating table. The closed envelope for this purpose contains a card for the report, and standard forms are provided for reporting the details of the status of the patient, of the operation, and of the follow-up. The importance of the central statistical unit cannot be overemphasized, since it has the responsibility of providing randomization instructions, indexing all patients admitted to the study, performing checks on the accuracy of the data, verifying survival periods, and, finally, assessing the effectiveness or lack of effectiveness of the experimental therapy. The results are being followed by a sequential method that allows early information and termination of the study if a statistically valid difference is observed. The pathology specimens are also centrally reviewed, at the Armed Forces Institute of Pathology.

It was estimated, on the basis of anticipated survival, that approximately 250 patients in the group receiving chemotherapy and 250 patients in the group not receiving chemotherapy should enter the investigation in order to reach the desired statistical determination of effect. In order to attain this number of patients within 18 to 24 months, 19 university departments of surgery and 20 Veterans Administration hospital departments of surgery are participating in the study. These groups are under the chairmanships of Dr. William P. Longmire of the School of Medicine of the University of California at Los Angeles and of Dr. John P. North of the Veterans' Administration Hospital in Dallas, Texas, respectively. The same protocol is used by both groups, and the results are statistically combined for analysis.

The participating surgeons meet at intervals to discuss their experiences and to clarify or modify the study plan as the group finds necessary. In all matters the safety and comfort of the patients is the paramount consideration. The poor prognosis of patients with gastric cancer should permit final assessment of the effectiveness of Thio-TEPA as an adjuvant chemotherapeutic agent against this tumor within two years after the necessary number of patients are entered in the study.

A second adjuvant chemotherapy study involves the use of nitrogen mustard in patients with resectable cancer of the lung. The study is quite similar to the one described for cancer of the stomach. The participants include 10 of the university surgical departments which are engaged in the gastric study, plus 8 other investigative groups and 21 Veterans Administration hospitals. The university group is under the chairmanship of Dr. Anthony R. Curreri of the Wisconsin University School of Medicine, and Dr. John P. North also serves as chairman of the VA hospitals' group on lung cancer.

Under consideration are additional studies on other sites of cancer, as well as the use of radioisotopes. The limited number of chemotherapeutic agents that demonstrate an effect on human cancer has restricted the present plans to the alkylating chemicals. It is obvious that any newer agents should first undergo wide trial in patients with cancer untreatable by customary techniques before they can be considered for use as adjuvants.


Patients with Clinical Diagnosis of Gastric Cancer or Gastric Ulcer
Ineligible to Continue in Study, Not subjected to Surgery
History - Physical, Pre-Operative Laboratory Studies
Eligible to Continue in Study Are Subjected to Surgery
Ineligible to Continue in Study Non-Resectable Cases
Placed in Therapeutic Category I or II Curative resections
Placed in Therapeutic Category III Palliative or Incomplete Resections
Category I
Category II
Sealed Envelope
Sealed Envelope
Sealed Envelope
Administer Chemotherapy «Treatment» Group
Do Not Administer Chemotherapy «Control» Group
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Conduct of study of stomach tumors in adjuvant chemotherapy program.

Two investigations are now under way, the first using Thio-TEPA (triethylenethiophosphoramide) in resectable carcinoma of the stomach and the second using nitrogen mustard in resectable carcinoma of the lung. Statistically controlled cooperative studies will expose a minimal number of patients to the effects of a toxic agent in a minimal length of time and provide accurate appraisal of its effect.

The use of chemotherapy as an adjuvant to surgical treatment of cancer has the theoretical advantage of testing the effect of an agent on small amounts of residual tumor and on unestablished tumor cells. A review of pertinent experimental work suggests that an agent that is moderately effective against an advanced tumor may be curative against smaller tumors and unestablished cancer cells.

Summary

Under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute, 27 university surgery departments and 21 surgery departments of Veterans Administration hospitals have developed a statistically controlled cooperative clinical study on the adjuvant use of chemotherapy in the surgical treatment of cancer.

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"DRY" BRONCHIECTASIS

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Bronchiectasis is generally accompanied by a chronic cough with purulent sputum and occasional hemoptysis; when neither sputum nor blood is produced, the bronchiectasis is called dry. Among the 22 cases of dry bronchiectasis here analyzed, there were 7 in which pulmonary symptoms were absent; the patients in the latter group requested medical examination for such nonpulmonary symptoms as failing vision, dizziness, or chronic fatigue. Three cases are given to illustrate the occurrence of hemoptysis, the episodes of dry coughing, and the occasional absence of respiratory symptoms. The diagnosis was established by roentgenograms, which were made in all cases. Surgical treatment was resorted to in but two of these patients, one because the amount of bronchial secretion was excessive and the other because there had been two episodes of hemoptysis.

Not all patients with bronchiectasis exhibit the classic symptoms of chronic productive cough, hemoptysis, and recurrent acute respiratory infections. A minority have minimal or atypical symptoms; a few are asymptomatic, the disease being discovered during investigation for some other complaint.

The present review, prompted by our recent experience with several such patients, is an attempt to assess the frequency of occurrence and the principal clinical manifestations of so-called dry bronchiectasis and to uncover possible distinctive anatomic features that might explain the absence of classic bronchorrhea.

The present study includes 22 cases of dry bronchiectasis encountered at the Mayo Clinic in the three-year period from 1954 through 1956. This total represents about 3% of the entire number of patients found to have bronchiectasis during this period. The clinical records of all patients who

From the Mayo Foundation (Dr. Gillis, Fellow in Surgery), and the Section of Medicine (Dr. Miller), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the graduate School of the University of Minnesota.

underwent bronchography during those years were reviewed, and those cases in which symptoms were atypical were selected for study. Posteroanterior stereoscopic roentgenograms of the thorax had been made in all of these patients during their medical examination. A bronchoscopic examination was performed in each instance in conjunction with, or on the day previous to, bronchography, so that the appearance of the bronchial mucosa and the presence or absence of secretion were noted.

Clinical Features

Ten patients were in the fifth decade of life, eight in the sixth, two in the third, and one each in the second and fourth decades. There were 8 males and 14 females.

Pulmonary History.—Eight patients had no history of previous pulmonary disease of any kind. Nine patients had had pneumonia, three during childhood and the remainder at some time during the preceding 10 years. Two patients gave histories of old and clinically inactive tuberculosis. One patient had had hemothorax of undetermined cause 2 years before, and one had experienced spontaneous pneumothorax 20 years previously. The remaining patient recalled having had pertussis in childhood.

Signs and Symptoms.—The clinical features were such that the patients could be classified into three groups. The first group included 13 patients who complained of previous hemoptysis, varying from one brief episode to recurrent bouts for several years; 3 of these patients also had chronic or occasional unproductive cough. The second group consisted of two patients who had only occasional unproductive cough. The third group comprised seven patients who did not have any pulmonary symptoms; they had requested medical examination for such nonpulmonary symptoms as failing vision, dizziness, or chronic fatigue. In the second and third groups of patients, abnormalities seen on routine roentgenograms of the thorax led to bronchoscopic and bronchographic studies that delineated the underlying abnormality. Routine roentgenography of the thorax showed abnormalities in only 6 of the 13 patients in group one. The history of hemoptysis prompted the endoscopic procedures in this group.

Physical findings were significant in eight patients, depression of breath sounds on one side being noted in five and transient rales in three. Examination of the thorax revealed no abnormalities in the remaining 14 patients.

Roentgenography.—Posteroanterior stereoscopic roentgenograms were interpreted as normal in 7 patients, with positive findings being noted in the remaining 15. The alterations varied from minimal increase in bronchovascular markings to changes that were sufficiently marked to suggest to the roentgenologist the likelihood of bronchiectasis.

As already indicated, bronchograms were made in all cases. The extent and distribution of the disease process varied considerably. The location of the bronchiectasis was as follows: Right lung—upper, 6; middle, 10; lower, 10. Left lung—upper 3; lingula, 6; lower, 9. Two or more lobes frequently were involved. Thus, the most commonly affected regions were the right middle and lower lobes, followed closely by the left lower lobe. It is generally accepted that bronchiectasis in the upper lobes has a tendency to produce fewer symptoms because of the natural bronchial drainage enjoyed by these regions. Thus, it is interesting to note that the upper lobes were not predominantly affected in this series.

In all cases in which the posteroanterior stereoscopic roentgenogram of the thorax revealed an abnormality, the bronchograms revealed bronchiectasis in the same zone. The disease was confined to this location in seven cases, while it was present also in other regions, sometimes on the opposite side, in eight others. In no case did bronchography fail to show disease in a zone designated as abnormal on the routine thoracic roentgenogram.

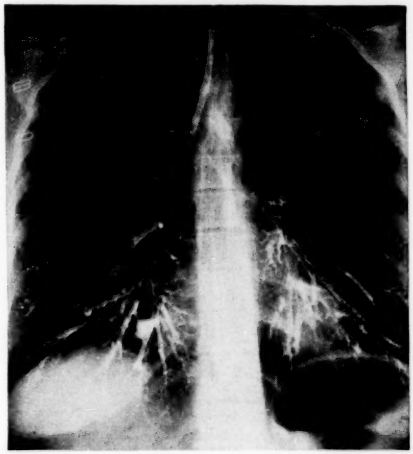

Fig. 1 (case 1).—Posteroanterior bronchogram revealing scattered saccular bronchiectasis involving bronchi in posterior basal segment of right lower lobe. The only respiratory symptom was occasional brief hemoptysis. The routine posteroanterior roentgenogram of the thorax was normal.

Bronchoscopy.—Bronchoscopic examination revealed no abnormalities in eight patients. In the remaining 14 cases, blood was detected five times, some distortion of the bronchial tree was noted on three occasions, and bronchitis was found in six patients. Five of these last six patients had an abnormal increase in volume of bronchial secretions; usually, however, this increase was slight.

Treatment

Resection of involved bronchopulmonary segments was done in only two cases, the symptoms in the others being so minor that the physician or the patient did not consider that a major operation was warranted. Hemoptysis occurring on two previous occasions was the indication for resection in one patient. Resection also was performed on an 18-year-old girl, the youngest patient in this series. She had had frequent winter colds and was found to have sinusitis and nasal polyposis also requiring surgical treatment. Bronchoscopy revealed the largest amount of bronchial secretions of any patient in this study. Although her only pulmonary complaint was "dry" cough, she obviously had been swallowing the excess secretions.

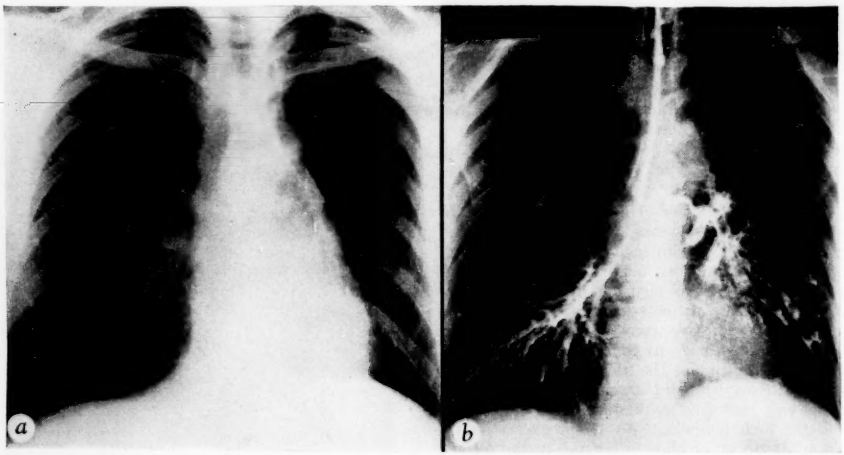

Fig. 2 (case 2).—*a*, posteroanterior roentgenogram showing mediastinal shift to left and some elevation of left hemidiaphragm. Scattered calcification is present, more prominent in the right lung field. *b*, posteroanterior view of bilateral bronchogram showing stenosis and angulation of left main bronchus with extensive bronchiectasis involving all major segments of left lung.

Report of Cases

The following three brief case reports represent the three types of presenting clinical problems encountered in this series, namely, hemoptysis (case 1), occasional dry cough (case 2), and absence of respiratory symptoms (case 3). Also of interest is the fact that examples of cylindric and saccular bronchiectasis are included.

CASE 1.—A 27-year-old housewife was referred to the Mayo Clinic in November, 1954, because of three previous bouts of scanty hemoptysis occurring in January and March, 1952, and in March, 1954. She denied having sputum except during colds. Physical examination revealed obesity but no other abnormalities. Bronchoscopy disclosed a small amount of inflammatory reaction in the bronchi of both lower lobes; however, not enough secretion was present to obtain a specimen for culture without preliminary bronchial irrigation with an isotonic solution of sodium chloride. Bronchograms using 20 ml. of iodized and chlorinated peanut oil (Iodochlorol) revealed saccular bronchiectasis involving the lateral and posterior basal divisions of the right lower lobe (fig. 1).

CASE 2.—A 43-year-old scout executive registered at the clinic because of lifelong difficulty with drainage from the left ear. This had been treated surgically four years previously by the surgical construction of a nasoantral window and by tonsillectomy and adenoidectomy. Mastoidectomy had been performed in 1946. Although he had experienced three attacks of pneumonia in the previous six years, he denied any cough except on rare occasions.

Physical examination revealed a moist cavity resulting from the left radical mastoidectomy. Profound deafness was present on the left, but signs of active local infection were absent. Breath sounds were diminished posteriorly over the base of the left lung. A posteroanterior thoracic roentgenogram showed the mediastinal structures to be displaced to the left (fig. 2*a*).

Bronchoscopy revealed slight narrowing and displacement of the left main-stem bronchus toward the midline. The bronchial secretions were not excessive. A dose of 20 ml. of propyliodone (propyl ester of 3, 5 diiodo-4-pyridone-*N*-acetic acid in water suspension with carboxymethylcellulose added [Dionosil]) in oil was instilled into each main bronchus; bronchograms revealed constriction of the left main bronchus, with bronchiectasis involving all of the segmental bronchi in the left lung (fig. 2*b*). The bronchi of the right lung were entirely normal. Cultures of bronchial washings were negative for acid-fast bacilli and fungi. Special studies did not reveal any malignant cells in the secretions.

CASE 3.—A 42-year-old woman requested examination while she was accompanying her husband, who was a patient, through the clinic. She complained of a constant tired feeling, worse in the morning on arising. Physical examination revealed a small nodular goiter but no other abnormalities. Routine stereoscopic roentgenograms of the thorax dis-

closed a shadow at the right cardiophrenic angle (fig. 3*a*). Because of the indeterminate nature of this asymptomatic intrathoracic lesion, bronchoscopy was carried out but it showed only normal tracheobronchial mucosa. A total of 28 ml. of propyliodone in oil was instilled into the right mainstem bronchus, and the resulting bronchogram revealed extensive saccular and cylindric bronchiectasis involving all divisions of the right upper and lower lobes (fig. 3*b*).

Comment

Bronchiectasis of varying distribution and severity can occur without causing the usual symptoms of cough with voluminous sputum or repeated bronchopulmonary infections. The criteria for making a diagnosis of "dry" bronchiectasis, as observed in the medical literature, are somewhat varied. The more liberal requirements include absence of a significant amount of sputum, whereas

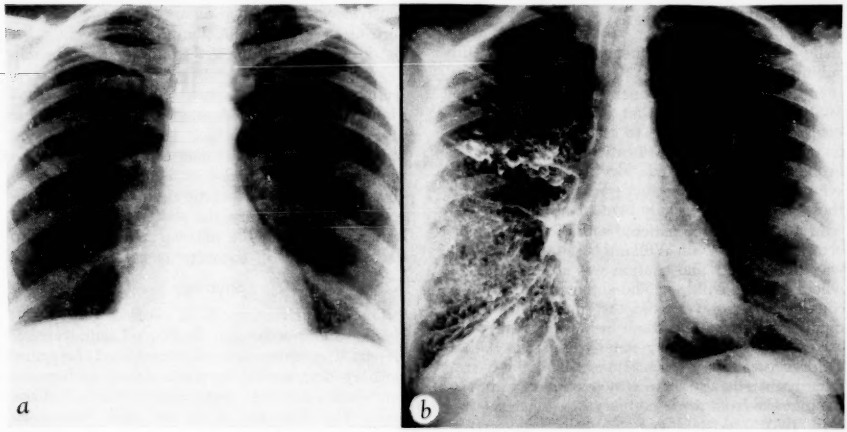

Fig. 3 (case 3).—*a*, routine roentgenogram showing asymptomatic density at right cardiophrenic angle. Slight fibrosis also is present in the right midlung field. *b*, right bronchogram revealing widespread bronchiectasis involving much of upper and middle lobes, as well as medial basal and superior segments of right lower lobe.

more rigid standards of finding bronchoscopically normal bronchial mucosa and absence of increased secretions also have been advocated.

The term apparently was used first by Bezançon and associates [1] in 1924, in describing two cases in which the only symptom was recurrent episodes of hemoptysis. In a review of 23 cases of bronchiectasis in children published in 1927, Findlay and Graham [2] stated that the disease may be present when there is no clinical evidence of its existence. However, a history of cough was elicited in all but one of their patients, and a history of the production of sputum was present in 19.

Pinchin and Morlock [3] described a series of cases of dry bronchiectasis in 1930. A clear history of antecedent infection was present in the majority of these. In the same year, Burrell and Trail [4] reported the case of a 23-year-old man in whom the first and only symptom of bronchiectasis was copious hemoptysis.

In 1933, Wall and Hoyle [5] reviewed all cases of dry bronchiestasis reported up to that time, a total of 30, and added 20 cases of their own. However, sputum was definitely absent in only 9 of their 20 cases, so their designation of "dry" is perhaps too liberal. These authors noted that the diagnosis of bronchiectasis in many of the previously reported cases was made in the course of an investigation of patients having bouts of unexplained hemoptysis.

In a review of 106 cases of bronchiectasis, Roles and Todd [6] used a classification that included "dry" types, but it is not clear just how many of their patients did not produce sputum. Bronchoscopic examinations, if performed, were not mentioned.

Warner [7] stated that the infection in a bronchiectatic zone may diminish gradually so that ultimately there is no bronchorrhea and a stage of dry bronchiectasis is the result. He noted that such cases were unusual and that they comprised only about 2% of his series.

In a study of 100 patients with bronchiectasis, Farrell [8] noted that 99% had a cough and 91% had sputum. He made no reference to dry bronchiectasis. Ogilvie [9] stated that persistent cough was an original symptom in all of his 68 cases; it was not productive in 8 cases. Although dry phases occurred in many of his patients, he concluded that he was unable to establish with certainty the existence of dry bronchiectasis. He emphasized further that the bronchial mucosa should be dry and uninfected, as demonstrated by bronchoscopy, be-

fore the adjective "dry" could be used correctly to categorize such cases; he was unable to demonstrate this in the eight cases in his series in which the cough was not productive, although bronchoscopic examination was not performed in four of them.

In 1942, Martin and Berridge [10] reported 25 cases of bronchiectasis in soldiers who were graded A-1 in the Army. Cough and sputum were the presenting complaints in 23, dry pleurisy in one, and evening fever in one. Only the patient with pleurisy was incapacitated.

Fine and Steinhausen [11] reviewed 41 cases of bronchiectasis discovered through the use of routine thoracic roentgenograms in service personnel. None of these persons were incapacitated, and 20 originally denied all symptoms. Follow-up studies were made in 36 of the 41, some for as long as two years. Of those, 8 had no symptoms and 20 had minimal symptoms. When the disease was originally detected, all of the men were performing full military duty.

In a discussion of bronchiectasis published in 1951, Overholt [12] stated that symptomatic bronchiectasis may be converted to a dry type if infection is overcome. In a classification of categories of bronchiectasis, he listed "dry types of minimal symptoms" and noted that the first evidence in these patients was usually hemoptysis.

In a report on 166 patients with proved bronchiectasis in 1953, Wynn-Williams [13] stated that cough was absent in 12 and sputum was absent in 24, of whom 12 were children. The author stated that the cough was less severe and the sputum smaller in quantity in his patients than in those in many other reported series. It is generally appreciated that children swallow bronchial secretions more frequently than do adults, who more often expectorate the material from the hypopharynx.

In 1955, Lindskog and Hubbell [14] reported a study of 215 cases of bronchiectasis. Patients with dry or asymptomatic bronchiectasis were not described as such, although minimal symptoms were noted as having occurred in eight patients.

Thus, it is apparent that many reports have included examples of dry bronchiectasis, although the incidence is always low. Not all authors used the term as originally employed by Bezançon and associates.

The practical implication of this and similar reports is that bronchiectasis may occur in patients who have no symptoms or who present symptoms unrelated to increased or retained bronchial secretions. A patient who has bronchiectasis and who coughs but does not expectorate may be swallowing sputum. However, most of the patients in our series did not have even a dry cough, or at least they denied it. Bronchoscopy revealed absence of bronchial inflammation or hypersecretion in 16 of the 22 patients. This would support the clinical feature of absence of cough in the majority of these patients. Five of the patients who were found to have excess secretion at bronchoscopy most likely were swallowing the secretions. Since the bronchial mucosa was normal and free of excess secretions in the majority of patients, some additional factor must account for the clinical absence of expectoration.

The reason for absence of an excess of bronchial secretions in this group of patients with bronchiectasis is not known. Furthermore, the exact mechanism of elimination of the normal and abnormal bronchial secretions is not precisely known. Ogilvie, in his extensive review, commented on numerous studies of the ciliary action and possible peristalsis of the muscularis in elimination of bronchial secretions. As early as 1929, Macklin [15] reviewed extensively the physiological studies on the musculature of the bronchi and lungs. More recently, the patterns of flow of mucus [16] and the rate of the ciliary beat [17] have been described as a result of newer techniques of investigation. As more is learned about these basic functions, an explanation of these atypical cases of bronchiectasis may be forthcoming. One can only speculate at present that the mechanism of elimination of secretions is either recovery in the bronchiectatic regions or, in the absence of such recovery, the ability of the bronchial branches distal to the affected zone somehow to decrease or resorb [18] the secretions.

Summary

The clinical features in 22 cases of "dry" bronchiectasis encountered at the Mayo Clinic were reviewed. Hemoptysis, usually considered the prime warning sign leading to discovery of such cases, was observed in only slightly more than half of the cases. The discovery of an abnormal pulmonary shadow in the thoracic roentgenogram in patients without respiratory symptoms was a common finding in this study. The combination of occasional nonproductive cough and an abnormal pulmonary roentgenographic shadow was the least frequent in this series.

The clinical picture of dry bronchiectasis was not related to the lobar or segmental distribution, the number of segments involved, the type of deformity of the segments involved, the age of the patient, or the history of previous tuberculosis. This syndrome accounted for only about 3% of all cases of bronchiectasis diagnosed during a recent three-year period.

Surgical resection of the involved pulmonary segments was advised only in two cases. Minimal or absent symptoms in most cases warranted only continued observation once the diagnosis was established.

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TREATMENT OF EIGHT CASES OF HYPERTHYROIDISM WITH COBALTOUS CHLORIDE

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and
Miguel Layrisse, M.D., Caracas, Venezuela

Eight patients with hyperthyroidism were treated with cobaltous chloride by mouth. Clinical improvement was manifested by abatement of the tachycardia, reduction of basal metabolic rate, and rise in red blood cell count and blood hemoglobin content in four patients. These four patients also gave striking evidence of improvement in laboratory tests with radioiodine and three of them underwent thyroidectomy without complication after the cobalt therapy alone. The other four patients had less favorable results. One showed improvement in her preexisting anemia but suffered recurrence (after temporary relief) of her symptoms of hyperthyroidism despite continued cobalt therapy; the other three did not respond to the cobalt at all as regarded their hypothyroidism, although one showed marked hematological improvement. The mode of action and indications for the use of cobalt in hyperthyroidism require further study.

Kriss, Carnes, and Gross [1] reported in 1955 the development of thyroid hyperplasia in four children and one adult receiving cobaltous chloride by mouth in doses ranging from 2.8 to 3.9 mg. per kilogram per day. In three subjects, in whom

TABLE 1.—*Chief Symptoms and Signs*

Case No.	Age, Yr.	Sex	Duration of Symptoms, Mo.	Loss of weight, Kg.	Nervousness	Exophthalmos	Goiter*
1	47	F	8	12	++	+	D1
2	24	F	12	30	++++	+	D3
3	24	M	24	15	++++	+	D3
4	50	F	48	++	++	+	D2
5	27	F	7	+++	++++	++	N3
6	22	M	3	30	++++	++	N2
7	38	F	1	++	+++	++	D3
8	13	F	7	++	++++	+	D2

* D=diffuse; N=nodular; 1=barely palpable; 2=palpable and visible; 3=grossly visible.

radioiodine (I^{131}) studies were done, it was found that thyroid I^{131} uptake was markedly depressed. Jaimet and Thode [2] have thrown serious doubts on those findings, since they were unable to demon-

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strate consistent effects of cobalt (in doses up to 6 mg. per kilogram per day) on thyroid I^{131} uptake, conversion ratios, and saliva radioactivity. More recently, however, Roche and Layrisse [3] have shown that cobaltous chloride in doses of 150 mg.

TABLE 2.—*Treatment and Clinical Course*

Case No.	Cobaltous Chloride, Mg./Day	No. of Days Given	Clinical Improvement	Apparent Increase in Goiter	Pulse/Min.* A	Pulse/Min.* B	Weight, Kg.* A	Weight, Kg.* B	Subtotal Thyroidectomy	Other Treatment
1	150 300	55 31	++++	0	130	80	53	53	+	Propylthiouracil; stopped 1½ mo. before cobalt started
2	300 0 150 300	3 1 8 34	++++	0	143	88	43	46	+	
3	300 300	30† 45	++++	0	100	80	61	61	+	
4	300 0 150	15 1 117	+++	0	100	80	41	44	...	
5	150 300	54 46	++	+++	130	94	39	46	+	Lugol's solution, 20 drops, t.i.d last 25 days
6	600 300	10 46	0	+	104	110	61	60	...	No response to methimazole or to perchlorate treat ment; finally controlled with 16 mc. of I^{131}
7	300 150 300	6 3 30	0	++	130	104	50	50	+	Response to methimazole
8	300 150 300	1 3 40	0	0	130	144	37	37	+	Response to methimazole

* A=before treatment; B= at the end of treatment.

† This patient was ambulatory during the first 30 days of treatment and it was felt that he did not take his medicament properly during this time.

per day in 12 nonanemic euthyroid adults led to a distinct fall in thyroid I^{131} uptake, in most cases after one week and in all cases after two weeks. In

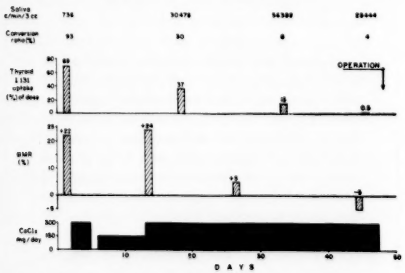

Fig. 1 (case 2).—Good response to cobalt therapy. Thyroidectomy.

view of these findings, it was deemed worthwhile to try cobaltous chloride therapy as a means of controlling hyperthyroidism.

Eight cases of hyperthyroidism treated with cobaltous chloride are herein reported. In four of the cases there was marked clinical improvement, and in three of these a thyroidectomy was performed without complication after cobalt therapy alone (cases 1 and 2 have been briefly reported[3]). In one case, there was initial response and later "escape," making it necessary to administer Lugol's solution before thyroidectomy; in the three remaining cases, there was no response to cobalt.

Methods and Material

Thyroid uptakes were determined with a scintillation counter (Nuclear, model DS-1), saliva radioactivity,[4] and conversion ratios [5] with a well-type scintillation counter (Nuclear, model 3037 B) 24 hours after the administration of 50 μc of I^{131}, correction being made if necessary for residual radioactivity. Cobalt was administered by mouth as cobaltous chloride in a 1% solution, in three divided doses after meals. The pulse was taken in the morning upon awakening.

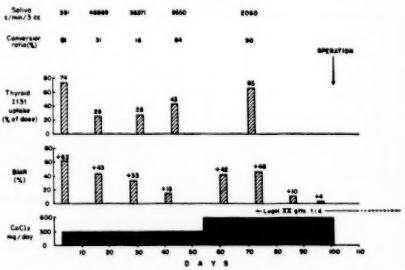

Fig. 2 (case 5).—Initial good response to cobalt therapy and later "escape." The administration of Lugol's solution in addition to cobalt led to rapid remission of the hyperthyroidism. Lugol's solution was continued after operation.

All patients were hospitalized in the Hospital Vargas. The chief symptoms and signs are given in table 1 and the treatment indicated in table 2. Histological study was performed on all thyroid glands removed at operation.

Results

The clinical course is summarized in table 2 and the chief laboratory findings before and at the end of treatment in table 3. Intolerance to medication in the form of epigastric pain, burning, and nausea was experienced by four patients, generally toward the start of treatment, while all other patients tolerated treatment well.

In one additional patient, treatment with cobalt could not be continued because of gastric intolerance to the drug. In the cases presented here, it was not necessary to discontinue medication entirely; in general, it was sufficient to stop cobalt for a day or two and resume therapy at a lower dosage

level. After a week or two, the dosage could be raised again to its initial level without further trouble.

Comment

In five of the eight patients with hyperthyroidism treated with cobaltous chloride, there was clear-cut remission of symptoms and laboratory evidence of blocking of thyroid hormone synthesis.

Although it is well recognized that hyperthyroidism may subside spontaneously, it is unlikely that this should occur in five cases out of eight during a relatively short period of observation. In the early reports collected by Sattler,[6] spontaneous remission is said to have occurred in from none to 50% of mild unoperated cases, with an average of 26%; recovery was described as usually occurring several years after onset. Since practically all patients today receive antithyroid treatment, there are no recent figures available on this point.[6] Furthermore, we do not believe that a spontaneous remission would explain the laboratory evidence of block of thyroid hormone synthesis.

It was possible to perform thyroidectomy on three of the five patients who responded to cobalt without the addition of any other antithyroid medication. In one of the patients, who objected to operation (case 4), it was possible to continue cobalt therapy for 117 days without any untoward effect. After medication was discontinued, there was no return of symptoms; the patient died two months later of a cerebrovascular accident.

evidence of block in thyroid hormone synthesis, and a decrease in basal metabolic rate (BMR) to normal levels. Thyroidectomy was performed 45 days after the beginning of cobalt therapy.

In one patient (case 5) (fig. 2) there was clinical improvement at first and evidence of thyroid block. After 30 days of treatment, pulse and nervousness

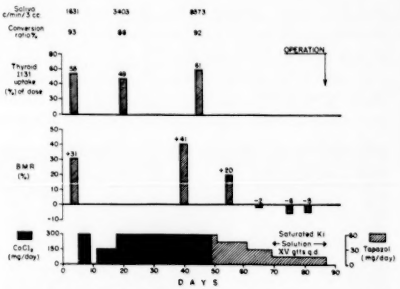

Fig. 3 (case 7).—No response to cobalt therapy. Good response to methimazole.

began again to increase and there was evidence of renewed thyroid activity; the goiter had increased markedly in size, and on the 70th day while cobalt therapy was being continued, Lugol's solution, 20 drops three times a day, was added, with resulting

TABLE 3.—*Effect of Cobaltous Chloride on Laboratory Tests*

Case No.	Blood Hemoglobin Level, Gm./100 Ml.*		Red Blood Cells, Million/Ml.*		BMR, %*		24-Hr. I^{131} Thyroid Uptake, %*		Conversion Ratio, %*		Saliva Radioactivity, 1,000 Counts/Min./3 Cc.*	
	A	B	A	B	A	B	A	B	A	B	A	B
Response												
1	13.3	15.0	4.2	4.7	+59	−1	78	17	76	5	5.3	53.9
2	11.5	15.0	3.9	4.4	+22	−5	69	0	93	4	0.7	56.4
3	13.8	17.7	4.4	5.1	+28	−6	51	17	92	6	0.2	61.2
4	10.4	14.0	3.5	4.3	+44	+1	76	1	89	7	0.3	125.7
Response and "escape"												
5†	11.7	15.0	3.9	4.5	+62	+46	74	65	91	90	0.4	2.0
No response												
6	13.1	14.3	4.5	4.5	+55	...	78	59	89	91	2.1	4.4
7	8.7	13.0	3.0	4.2	+31	...	55	49	93	86	1.6	8.5
8	9.1	9.1	3.3	3.0	+44	+21	58	42	93	87	0.8	5.6

* A=before treatment; B=after treatment with cobalt.
† This patient "escaped" treatment. The levels reached before escape were BMR, +15; thyroid uptake, 26; conversion ratio, 16; saliva radioactivity, 48.9.

The data on one of the patients who responded to cobalt (case 2) are presented in figure 1. In this case, the initial dose was 300 mg. of cobaltous chloride per day. This had to be stopped after three days because of nausea and epigastric distress. After 24 hours off treatment, cobalt therapy was resumed, at a dose of 150 mg. per day, without difficulty, so that after a week the initial dosage could again be started. There was definite clinical improvement after three weeks, associated with rapid and marked clinical improvement. Thyroidectomy was performed within 30 days of starting therapy with Lugol's solution. It is interesting that this patient had a nodular goiter, in which resistance to therapy is frequently observed.

Finally, in three cases, there was no response to therapy, even though cobalt was given in doses similar to those given in the previous four cases. The data on one such patient (case 7) are shown in figure 3. In spite of the administration of cobalt

for 45 days, there was no change in clinical status, thyroid uptake, conversion ratio, BMR, or saliva radioactivity. Treatment with methimazole (Tapazole) resulted in rapid improvement, and thyroidectomy was performed after the addition of saturated potassium iodide solution. One of the three patients who did not respond to cobalt (case 6) had also a nodular goiter, and there was no response to drug therapy with methimazole or with potassium perchlorate. Hyperthyroidism was finally controlled in this case with 16 mc. of I^{131}.

In all of the patients who responded to cobalt, blood hemoglobin levels and red blood cell counts rose under therapy (table 3). Of the three patients

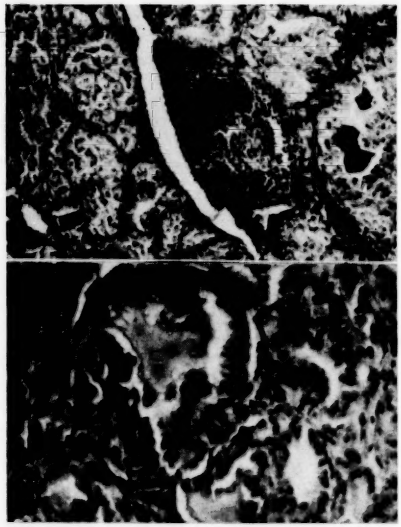

Fig. 4.—*Top*, thyroid tissue from patient in case 2. Thyroid hyperplasia, high epithelium, sparse colloid; in the center, accumulation of lymphocytes (hematoxylin-eosin stain, × 150). *Bottom*, thyroid tissue from patient in case 1; infolding epithelium; sparse colloid with abundant vacuoles (hematoxylin-eosin stain, × 300).

whose thyroid status did not change with cobalt, only one (case 7) showed a distinct rise in hemoglobin and red blood cell count, but this could not be attributed to cobalt, since this patient was given ferrous sulfate therapy simultaneously. The lack of response in the hematological indexes of two patients (cases 6 and 8) would suggest that, in these cases at least, cobalt was not properly absorbed and therefore did not reach in sufficient concentration either the thyroid gland or the bone marrow.

Histological study of the thyroid glands removed at operation (fig. 4) after cobalt treatment alone showed marked hyperplasia of follicular tissue with a high columnar, infolded epithelium. The sparse colloid contained abundant vacuoles. This appearance is not unlike that seen in patients treated with antithyroid drugs of the thiouracil type.

Cobalt appears to be clearly capable of blocking thyroid hormone synthesis in hyperfunctioning thyroid glands, as it does in normal thyroid,[3] although its action is somewhat unpredictable, as witnessed by the three patients who showed no response whatever. The reason for this lack of response is at present unclear, as is in fact the mechanism of cobalt action on the thyroid. We feel, however, that, in view of the good results obtained in several of the cases, it might be interesting to submit this drug to further therapeutic trial in hyperthyroidism.

Summary

Eight patients with hyperthyroidism were treated with varying doses of cobaltous chloride by mouth. In four of these, there was marked clinical improvement and evidence of block of thyroid hormone synthesis. In three of these cases a thyroidectomy was performed; the histological appearance was that of follicular hyperplasia. One of the four patients who responded was carried for 117 days on cobalt therapy, with apparent clinical remission. One patient who responded initially later "escaped" the effect of the drug and had to be given Lugol's solution before operation. In three cases, there was no response to the drug; one of these patients did not respond to methimazole or potassium perchlorate, and had to be given I^{131} therapy.

Apartado 1827 (Dr. Roche).

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MOBILE EEG DIAGNOSTIC UNIT OF THE MICHIGAN EPILEPSY CENTER AND ASSOCIATION

Adele L. Rolfe, M.S.W., Arthur J. Derbyshire, Ph.D.
and
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The total mobile unit service of the Michigan Epilepsy Center and Association (MECA) includes electroencephalography (EEG), neurological consultation, neurological examination, and lectures on epilepsy. From the physician's referral information and the patient's previous medical and hospital contacts and social-medical history, the neurologist adds to the EEG report his diagnostic considerations and suggestions for the continued management of the patient. The referring physician therefore receives both the EEG report and neurological consultation. The very presence of this diagnostic laboratory in an area tends to strengthen the patient-doctor relationship in many instances. One major problem for the mobile unit, which is still not satisfactorily solved, concerns the ideal for which the MECA stands, namely, a total approach, with use of many medical and allied disciplines to determine the causes and the treatment program for each patient.

In 1947, the Michigan Epilepsy Center and Association (MECA) came into existence with a grant from the Society for Crippled Children and Disabled Adults, through its state organization, Detroit and Dearborn Chapters. Three years later the Michigan United Fund assumed the support of the center. This change brought with it increased responsibility to the residents of the state of Michigan for service in the area of epilepsy. Dr. R. Dixon, who was our medical director at that time, and who had recently retired as medical superintendent of Caro State Hospital for Epileptics, suggested a traveling electroencephalography (EEG) service. At that time only two of the four EEG centers in the state were open to use by general practitioners, and these were below the center of the state. There were, however, rumors of the establishment of two additional EEG facilities. In fact, in accordance with the distribution of the population of the state, about 50% lived outside of counties with EEG laboratories. Dr. Dixon's suggestion was to put an EEG unit into a suitable truck and tour the areas of Michigan where EEG service was not readily available. In the summer of 1951 under the direction of Mrs. T. E. Kidder, a traveling EEG unit was put on the road for the first time.

One major problem of our program for the mobile unit, which is still not satisfactorily solved, concerns the ideal for which the MECA stands, namely, a total approach, using many medical and allied disciplines to determine the causes and the treatment program for each patient. A mobile EEG service tends to deny this and perhaps places the EEG in the dubious position of being called upon to form the sole basis for diagnosis. What it can accomplish, however, far outweighs these deterring aspects. This program can (1) offer the medical practitioner the information gained by EEG for the benefit of the patient (the test will confirm his impressions, help in evaluating severity of disturbance, and find possible foci for seizures, as well as contribute to treatment plan); (2) increase the awareness of the physician in treatment possibilities; (3) increase the understanding of the general population about epileptic people and their illness; and (4) encourage, through its use, interest in developing additional local EEG facilities as permanent installations.

Administrative Director of State-Wide Mobile Program (Miss Rolfe); Chairman of the Research Planning Team and Consulting Neurophysiologist (Dr. Derbyshire); and Medical Director (Dr. Bohn), Michigan Epilepsy Center and Association.

Around any such permanent installations stimulated by the mobile program the center can develop the total approach, as it has been developed in Detroit. Here, each referred patient is seen by a neurologist, an internist, a psychiatrist, a pediatrician, a neurophysiologist, a social worker, a psychologist, and a religious consultant. Through mutual discussion, their information about the patient is synthesized into a diagnosis with probable etiologies and appropriate treatment recommendations covering all areas studied.

While falling far short of such a total study, the mobile unit has added, as money has become available, neurological consultation. It has always been the hope to broaden the approach through permanent facilities, or, as a second choice, to expand the mobile services.

Method

Description of Mobile Laboratory.—Finances limited the traveling program to a 10-week period, and weather conditions throughout northern Michigan, which was our primary target, limited the program to the summer. Finances further limited us to producing an EEG technician who was also a truck

driver with a chauffeur's license. Finances again limited us to a moving vehicle of such size that it could be sleeping quarters, office, and EEG laboratory, all in one. A friend of the center, hearing of our needs, offered us the loan of a new 2½-ton trailer of the type used for moving furniture; we would have to rent the tractor. In this large van

Fig. 1.—Mobile unit parked behind hospital.

were such items as a cot, a large easy chair for the patient during the EEG test, an eight-channel Grass EEG instrument, a table, and chairs.

The following year this mobile equipment was replaced by a house trailer and a pickup truck, and in 1954 we were given the present equipment (fig. 1 and 2), which consists of a paneled single-unit truck, donated by a large electrical manufacturing firm. This truck, 30 ft. long by 8 ft. wide by 11 ft. high, was originally custom-built in Ohio for the purpose of displaying electrical equipment. We easily adapted it to our use by dividing the space with a curtain into living and working quarters for two people. It can be driven into any small hospital or clinic grounds, where the unit can obtain water through a 100-ft. hose and its needed 2,000 watts of 110 AC power through a 100-ft. electric extension cable. As assurance against power failure, there is a gasoline-driven generator in the rear of the truck, which can supply enough power with adequate frequency (60-cycle) control to obtain reliable recordings. Derryberry [1] describes a similar truck used for mobile chest x-rays.

The Grass Instrument Company supplied us with a special rubber mounting, such as is used for fastening an engine block to a chassis. Through this, the EEG instrument is bolted to the floor during transportation. It can be unbolted and wheeled about the truck once the unit is parked. The problem of electrical grounding is solved by connecting the ground post of the EEG instrument to the metal structure of the truck. This uses the grounded side of the AC supply as the one common grounding point for both the EEG instrument and the metal body of the truck. The metal body, therefore, becomes the electric shielding. The only troubles which develop occur when the unit is parked under a transformer or when in a heavy rain a double ground is made by the water rising to contact some metal part or wheel of the truck. In most situations less artifact of 60-cycle pickup is encountered than in many hospital laboratories.

In selecting personnel to operate the mobile unit, it has been our experience that the most interested and resourceful technician can be developed in medical or premedical students. The job offers them opportunity to learn more about neurophysiology, history taking, and patient contact and invaluable experience in working with established medical practitioners throughout the state where the medical student is eventually most likely to practice.

We receive in return, from the medical student, a dedicated kind of interest in patients. They have an enthusiastic and warm center-doctor relationship, an insatiable curiosity to develop their understanding in the area of epilepsy, and a medical orientation and vocabulary for this work.

Services Offered.—The total mobile unit service includes EEG, neurological consultation, neurological examination, and lectures on epilepsy. The EEG service offers a standard half-hour test, which can reveal a localization as well as description of general pattern. In addition, activation is often tried, with use of hyperventilation and/or sleep following sedation. Practically any variation of the EEG test

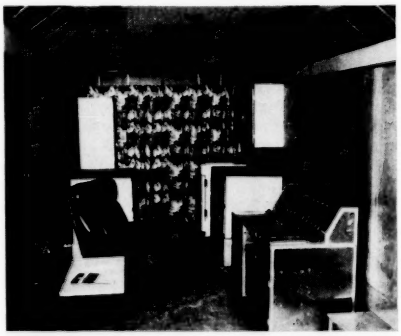

Fig. 2.—Inside of truck looking toward back from co-driver's seat. Curtain shuts off back windows. On right-hand wall are eight-channel electroencephalograph, cabinets for kitchenware above and clothes below, and combination sink, two-burner stove, and refrigerator. At left are chair used for patient during EEG, more storage cabinets, and clothes closet. By moving curtain into position behind EEG instrument, working and living quarters can be separated.

is possible if requested by the referring physician. For example, if the doctor wishes an EEG study to be made in relationship to a glucose tolerance test,

the blood tests can be done in the hospital laboratory concurrently with brief EEG tests of 10 minutes' duration once every hour.

All EEG records taken on the road are mailed to Detroit, where they are read by the neurophysiologist. This report is then given to the neurologist who, by this time, has a complete folder on each patient. It contains a statement from the referring physician relative to present medication, seizure occurrence, and particular problems of management. There is also available to the neurologist a birth record, a detailed history form filled out by patient or parent, and copies of reports from previous hospitalizations or specialized treatments.

From all of this material, the neurologist adds to the EEG report his diagnostic considerations and suggestions for the continued management of the patient. The referring physician therefore receives both the EEG report and neurological consultation. Of the 150 to 200 patients examined each summer, there are occasional problems which require more detailed study. In these instances, the neurologist recommends and offers the physician the further service of a neurological examination of the patient. Neurological clinics are then scheduled at central locations, where the referring physician, neurologist, and neurophysiologist have an opportunity to examine the patient together and to decide upon

Fig. 3.—Route taken for summer of 1957. Counties serviced are stippled.

further procedures. What hospital or other facility he will choose to carry out these further recommendations is left to the discretion of the referring physician. Occasionally, these mobile services stimulate a county medical society to invite the center's staff to an evening meeting. The staff shares its extensive experiences in the field of epilepsy through the discussion of representative patient problems.

Relations of Center to Patients and Physicians.—The method by which this service reaches the patient and physician has been solved by a somewhat unique procedure. Through the counselors of the Michigan State Medical Society, the services are

Fig. 4.—Counties covered, 1951-1957. Numerals show total number of visits to each county from 1954 through 1957. Areas without visits (*blank*) are serviced by stationary EEG laboratories. Most frequent visits are to Upper Peninsula area because it is furthest from stationary EEG facilities.

made known to each county medical society. Then, through any interested county medical society, we receive an invitation to bring the mobile service into its area. A letter is sent from the center to each member of the county medical society requesting service, inviting him to refer any of his patients suspected of having convulsions. Upon receipt of the doctor's referral, each patient is contacted, given a history form to fill out, and advised of the time, place, and date for the EEG study.

Administrative Aspects of the Program.—Selection of areas to be covered, contact with county medical societies, and contact with the referring physicians must be done months before the mobile unit begins its 10-week trip on the road. It is important that any group considering a mobile program like this be cognizant of all the planning and administrative procedures that accompany this prelude to the actual summer's trip.

The budget preparation and its justification to the Michigan United Fund are the responsibility of the executive director (R. D. Dennerll). A physician (H. B. Zemmer), as chairman of the state-

wide mobile committee of our board of directors assists in planning the areas to be covered. He also interprets to the officers of state and county societies the services of the mobile program. The voluminous correspondence and the creation of the precise route and schedule are the responsibility of one of us (A. L. R.) throughout the six months before the unit leaves Detroit (fig. 3). In planning a summer's route, we take account of the areas of first requests and areas covered during the last two years, as well as the probable needs of each community. It is desirable to cover all the areas of the state without EEG facilities at least once every three years and to cover them in such a way that the 10 weeks is neither overprogrammed nor underprogrammed.

Responsibility for the medical service rests with one of us (Z. S. B.) as the center's medical director. The education department at the MECA maintains from the inception to the completion of the program a liaison between the center and the communities being served through such mediums as newspapers and radio.

Summary of Mobile Unit Program

Yr.	Counties Served	M.D.s Contacted	M.D.s Referring	Patients Seen	Unit Stops	Mileage
1951.....	11	482	53	95	8	1,329
1952.....	17	90	34	96	5	1,007
1953.....	17	82	34	71	5	682
1954.....	26	396	57	175	8	1,184
1955.....	20	203	60	150	8	1,281
1956.....	14	341	49	123	8	1,301
1957.....	21	399	72	190	10	1,271
Totals...		1,993	359	900	51	8,055
Averages per year.	18	285	51	129	8	1,151

An average of 18% of the doctors contacted referred about 2.5 patients each.

Results

Areas Covered.—In the seven years of mobile unit operation, 54 counties out of a total of 83 have received the service. After about two years, we found that particular localities, especially in the Upper Peninsula, were looking to the center for repeated EEG service. In fact, 12 out of the 15 counties (80%) in the Upper Peninsula have requested and received service for three or more years (fig. 4), compared to 5 out of 39 counties (13%) in the Lower Peninsula during the same seven-year period.

The table represents a summary of the number of counties serviced each year, the number of physicians invited to refer patients, the number who actually made referrals, the number of patients who received the examination, the number of stops made, and the distance the unit traveled. One important problem not revealed in the table is the problem of scheduling appointments and determining the number of days the unit must remain in any stop. It has been our experience that the anticipated number of patients scheduled often differs from the actual number referred, once the unit has arrived. In 1957, we anticipated 147 patients and were asked to see 190. The same summer, the number of physicians who indicated their intent to refer patients before the unit left Detroit was 48. However, the total number of referring physicians at the end of the summer was 72.

Financial Problems.—A charge of $30, which this year represents one-half of the total cost per capita, is asked of each patient with the request that he pay all, or as much as is possible, of this minimal charge. The other half of the cost, which is not asked of the patient, plus whatever part of the $30 he does not pay, is absorbed as part of the operating budget supplied by the Michigan United Fund. The patient is informed that it is the voluntary contributions of the people of Michigan through the Michigan United Fund that makes up this difference. The cost of the mobile program to the center, including prorated administrative expenses, was $12,270 in 1956 and an estimated $13,750 in 1957. Total reimbursement in patient fees was $1,877 in 1956 and $1,760 (to the time of writing) in 1957.

Comment

Implications of EEG Study.—A first concern was to determine if the EEG made in the mobile laboratory was equivalent to the routine EEG in quality. By inspection it appeared to be as free of confusing artifacts as any being currently taken in Detroit. The techniques, electrodes, and length of record were identical. Therefore, the differences and similarities are discovered by comparing the profile of frequency of occurrence of each rating for three sources of patients (comparison groups). These consist of (1) the records from the mobile program; (2) records from the Detroit laboratory of the MECA; and (3) records from a private, voluntary, nonprofit hospital (Harper Hospital). In figure 5*A* is shown the EEG ratings on a five-point scale [2] for the three comparison groups of records. All records were read and rated by the same person (A. J. D.); consequently we can compare the EEG ratings from the three sources. The pattern is the same. In fact, the curves for the traveling records and for those referred to a general hospital are almost identical. The patients sent to the center, however, show a greater number of more disturbed EEG patterns, while those at the private hospital show the least disturbance. To further understand these relations and to further evaluate the reliability of this comparison, the distribution of ages in five-year blocks was compared for these comparison groups. The number of patients found in each age group is expressed as a percentage of the total number of patients in each comparison group. This relationship is graphed in figure 5*B*. The per cent population at 5 to 9 years of age was arbitrarily chosen as the point at which the three

distribution curves were made equal. This point was chosen because it tended to place the three curves most nearly together for less difficulty in comparison. The comparison brings out that all three distributions are similar between 5 and 34 years of age.

The greatest proportion of patients from 0 to 4 years of age is found in the Harper Hospital population because of its large pediatric ward and the many pediatricians on its staff. These 0-to-4-year-old patients are next most commonly found in referrals by general practitioners to the mobile unit. Since both the above groups are reluctant to consider the diagnosis of epilepsy until the patient is older, the center receives the lowest percentage of these patients (infants).

From 35 years of age and over, another deviation occurs. The patients of these older age groups are more commonly referred to the mobile unit and to the general hospital than to the center. This probably is the result of the generally held knowledge that in older patients the onset of seizures most likely is related to organic illness. The tendency, therefore, would be to send a patient in this age group to a neurologist or general hospital, and not to an epilepsy center. Like the general hospital, the mobile unit receives these cases because of the lack of specialists in neurosurgery and neurology in rural areas.

Implications of Traveling Program in Medical Practice and Doctor-Patient Relationships

Diagnostic Implications.—Inasmuch as all patients are referred to the mobile unit by their doctors and because we have the referring physician's material concerning the patient as well as records of his previous hospitalizations, we are in an excellent position to review the medical management prior to the time of the request for EEG and neurological consultation. We find, on the whole, a high degree of excellence of medical practice with convulsive disorders. These physicians use a wide variety of drugs and combination of drugs. The drugs are not always given up to maximum needs for seizure control, but seldom do we find cause to recommend use of different drugs. In some instances, our study may correct, or help clarify, the type of seizure that would necessitate the addition or change to a specific drug of choice for that particular type of seizure. Also, our experience may help the doctor focus treatment in areas other than medication, which also need consideration for seizure control.

Doctor-Patient Relationship.—It has been our experience that the very presence of this diagnostic laboratory in an area tends to strengthen the patient-doctor relationship in many instances. The doctor has something tangible to offer his patient. Too, he has the opportunity to review his patient's progress with the neurophysiologist and neurologist. The patient, in turn, may read of the unit's arrival and is rekindled with new hope so that he returns to his doctor after prolonged absence. In those counties visited in successive summers, we find a closer relationship between the doctor and his patient with seizures, both working toward better seizure control until another "repeat" EEG can be obtained. In this way the attitude of hopelessness, which stems from both the physician and the patient with uncontrolled convulsions, can be changed. Renewed interest and hope offers the opportunity for continued help, newer medications, and a stronger doctor-patient relationship.

Review of Therapeutic Progress.—Annual availability of modern instrumentation to the doctor and to his patients encourages repeated review of therapeutic progress and reduces postponed study. It has acquainted the physician with the use of EEG—its values and its weaknesses—in answering clinical questions. We are impressed that the same questions are behind the medical referral, regardless of the patient's location in the state: 1. Is this

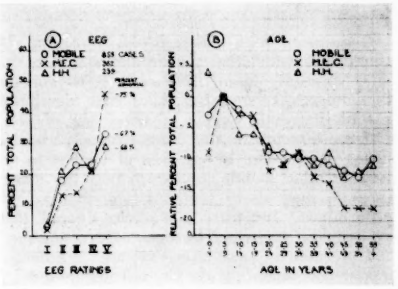

Fig. 5.—A, comparison of EEGs from three sources on basis of five-point rating. I=perfectly normal; II=normal; III=borderline normal and borderline abnormal; IV=abnormal; and V=diagnosably abnormal. H. H.=ratings of 239 consecutive cases referred to private hospital with diagnosis of possible convulsive disorder. M. E. C.=ratings of 352 consecutive cases referred to MECA in Detroit for full-team diagnostic examination. These patients have usually had diagnosis of convulsive disorder for some time. Mobile=ratings of 855 cases referred to mobile unit over last seven years. Percentage of abnormal patients gives proportion of patients rated V, IV, and III borderline abnormal. Values in percentage are placed opposite to end of curve representing those data. *B*, comparison of distribution of age of patients referred to three sources used in *A*. Percentages were all made equal at 5-to-9-year range and each plotted as differences from that value.

a convulsive disorder as I suspect? 2. Can this patient be taken off medication now that his seizures have been controlled for two years? 3. What kind of medication would help this patient? 4. Are there other factors, such as emotions or somatic disturbances, which contribute to this patient's seizure occurrence? 5. What capacity does this patient have for such aspects of living as school, marriage,

driving, and working? 6. What are the evidences for some organic disturbance from trauma, infection, or neoplasm as an underlying cause?

As a rule, the report from the center tends to increase the number of patients with "symptomatic" convulsive disorder, as against the essential, or "idiopathic," disorder. We have reduced medication in the well-controlled patients, but, in general, we tend to recommend continuing minimal doses for a longer period than the referring doctor often does. We rarely find reason to disagree with the referring physician's diagnosis.

We constantly attempt to increase the patient's functioning within the range of reality. In one location, 12 recommendations were made concerning seven patients directed toward expanding each patient's social and physical activities. Even with our limited studies, we do find inescapable evidence in 20% of these patients that disturbances in the emotions and in such somatic processes as sugar, water, and energy metabolism contribute to the problem. Both tests and treatment recommendations are suggested in these cases.

Comparison with Other Mobile Programs.—A comparison with other mobile clinics and health units shows significant differences. It is probable that others, like ourselves, have each developed special diagnostic, public relations, and physical features directed to the solution of a particular illness or problem. It has been of interest in reviewing other mobile services to note the differences in methods of transportation, that is, airplane,[3] boat,[4] and truck [5]; in service offered, that is, complete or partial treatment [6] or diagnostic [7] and preventive [8] medical service; and in administration and financing, that is, private,[9] hospital,[5b] government,[10] and voluntary.[11] In none of this extensive review of the literature has there been any previous publication describing a mobile clinic using a delicate EEG instrument. We know that early EEG amplifiers were transported from place to place by Gibbs [11a] in the mid-30's, later in World War II by Schwab,[12] and finally in the Korean war by Caveness.[13] Dr. Caveness had a mobile unit aboard ship.

In review of other mobile programs, we have found that many different methods have been used successfully to relate the mobile program to the local doctor and his patient. These are determined by the financial backing, the finances of the group serviced, and the available local medical facilities.

Implications of Program for Community and MECA

Long before the actual presence of the traveling unit in a community, its arrival is anticipated from agencies whose record pertaining to a patient has been requested by the Detroit center. These agencies then in turn look to the test results as supplementing their information and offering them assistance in their planning for the patient. These agencies are as numerous as they are wide in scope. They may represent the epileptics' interest in school, vocational training, eligibility for Old Age Survivors Insurance benefits, eligibility for guidance and counseling, a legal decision, and many other areas. Obviously, an EEG and neurological consultation cannot offer answers in all of these areas, nor can the report always present an adequate appraisal of the person's individual capabilities. It would be as unfair to use an EEG rating for the sole determination of a patient's capacities as it would be unfair to judge a person according to his IQ rating alone. We do feel that much more needs to be done in making our usefulness felt by social agencies in a community and in the same way gaining from them their particular kinds of information that would help us better to understand a patient's needs, his pressures, and, therefore, his seizures.

However, the problem of answering the many and varied questions raised by the local resources is not solved by mere exchange of information. This is the case whenever the limitation of getting information exists within the program itself. What answers we can give, plus repeated visits to some areas where the physicians have had opportunity to obtain an annual review of their patient's seizure activity demonstrated by EEG, has aroused interest within these communities for permanent facilities to provide a more complete evaluation of the patient. We are encouraged by this attitude and interest. It reflects again the need for studying the epileptic completely, as has been demonstrated for 10 years at the Detroit center.

It has been our experience that the number of referrals to the Detroit center for the complete physical-emotional-social diagnostic evaluation has increased within the areas visited by the mobile unit. Some patients and physicians have felt that the 200 or 300 miles traveled to Detroit is a negligible factor for the information necessary to plan adequately for a patient's treatment program. Again, it is a demonstration of the need for establishing permanent centers in those areas now alert to the value, as well as the limitations, of EEG and, more important, alert to the treatment possibilities now recognized for helping the epileptic.

Summary

Since 1951 the Michigan Epilepsy Center and Association (MECA) has had a mobile electroencephalography (EEG) laboratory. An eight-channel EEG instrument is mounted in a suitable truck and driven over 1,000 miles during a 10-week period each summer. Stops for the mobile unit are arranged prior to the date of departure, and areas visited are determined by invitation from the

county medical societies. EEG studies are made on appointment arranged with the patient at the request of his physician.

The EEG tracings are read by an electroencephalographer. Their accuracy is compared to those obtained at permanent installations at the MECA and at a private hospital. The neurologist at the MECA reviews the EEG readings, the patient's history, copies of previous medical reports, and data from the physician. A copy of the EEG report and the neurologist's suggestions pertaining to management are returned to the referring physician.

This paper describes the administrative problems, costs, geographical distribution of service, and a comparison with other mobile clinics. It discusses the implications of this program with regard to the doctor-patient relationship and to the community. The EEG mobile clinic makes available to an area with a widely scattered population and little concentration of resources this relatively expensive EEG instrument, trained personnel, and technical procedure.

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DIABETES IN THE AGED.—First, let me say a word about the incidence of diabetes and its detection at all ages. Approximately 1 per cent of the population has it, and another 1 per cent has it but does not know it. In the wards of hospitals in Boston which we recently surveyed, in a twelve-month period there were 500 patients with surgical lesions of the foot who proved to have diabetes. Ten per cent of them admitted no previous knowledge of the disease. The cost of that group of cases is tremendous, not merely in terms of dollar costs paid by the patient, but in terms of medical and surgical time. The diagnosis of diabetes is still a problem. A good test for sugar in the urine does not exist. With present procedures, a frank case of diabetes can be detected, but not a borderline case. We still are hampered by inadequacies of the fasting blood sugar method. In 1954, five hospitals in Boston tried the experiment of determining the blood sugar level of middle-aged patients without diabetes, one hour after breakfast. Five per cent of the first 300 patients had diabetes which was unrecognized and untreated simply because they had been tested previously by the fasting blood sugar method—which is sure to miss in some cases of diabetes.—Howard Root, M.D., Panel Discussion on Diabetes Mellitus in the Aged, *Journal of the American Geriatrics Society*, June, 1957.

CLINICAL NOTES

SIMPLE INSTRUMENT FOR EVALUATING PULMONARY VENTILATORY FUNCTION

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and
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The measurement of vital capacity alone is rarely adequate for estimating ventilatory function.[1] Several other tests, such as maximum breathing capacity and residual volume determinations, are often additionally employed in pulmonary function studies. The maximum breathing capacity test, though a dynamic pulmonary function test, has many shortcomings.[2] The apparatus is cumbersome, and the procedure is fatiguing to incapacitated patients. Other more elaborate pulmonary function tests usually require expensive equipment and skilled technical knowledge, and they are often time consuming. Such tests frequently require special facilities which are available in pulmonary research laboratories and not to the average practicing physician.[3]

By attaching a solenoid and an interval timer to the standard vital capacity spirometer,[4] Gaensler constructed a simple instrument for the measurement of both the total and the timed expiratory capacity from 1 to 10 seconds. The one-second expiratory capacity, expressed as per cent of predicted total vital capacity, was found to correlate very closely with the maximum breathing capacity similarly expressed.[1a] Segal and associates[5] described the use of a vital capacity timed interval ruler for the measurement of the timed expiratory capacity in conjunction with the Collins respirometer. Franklin and co-workers[2b] suggested the clinical use of tracings of forced expiration. Recently, Worton and Bedell[6] reported the use of a gas meter as a substitute for the spirometer for the measurement of vital capacity and maximum breathing capacity.

For evaluating bronchodilator drugs, Cander and Comroe[1b] introduced the use of maximum expiratory flow rate (MEFR) as a measurement of the expiratory resistance. They employed a Benedict Roth type of spirometer which was made to record on rapidly moving kymograph paper. The MEFR, expressed in liters per minute, was calculated from the time required for the expiration of 1 liter of air measured from the 200-cc. to the 1,200-cc. volume on the spirometer calibration curve. To achieve greater compactness and portability, Johnston and one of us (R. E. S.)[7] attached a synchronous timer and means for recording simultaneously the time and the angular displacement of the bellows of a McKesson-Scott vital capacity machine.

The present paper is concerned with an improved apparatus based on the same principle but offering greater convenience of operation and ease of computing MEFR, timed expiratory capacity, and total vital capacity. Construction detail, procedure for operation, method for computing measurements, and sample tracings are also presented.

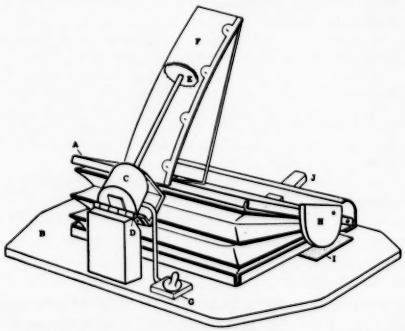

Fig. 1.—Recording spirometer apparatus, illustrated with bellows in partially inflated position. *A*, lid of McKesson-Scott vital capacity apparatus; *B*, flat board; *C*, clock; *D*, hinge; *E*, gear; *F*, supporting plate holding record strip; *G*, switch; *H*, cam; *I*, sandpaper; *J*, mouthpiece.

The Apparatus

Construction of Apparatus.—The design of the apparatus is aimed toward achieving the following features: (1) measurement of timed and total expiratory capacities and MEFR simultaneously and accurately after one single forced expiration; (2) inexpensive cost of construction, operation, and maintenance; (3) simplicity in conducting the test

From the Lilly Laboratory for Clinical Research, Indianapolis General Hospital.

and computing results; and (4) permanent records of performance which may be included in patients' charts for later comparison.

The McKesson-Scott vital capacity apparatus is used as a receptacle for expired air and is supported by a flat board, at one end of which the recording assembly is mounted (fig. 1). The time-recording device consists of a synchronous clock motor, to the shaft of which is mounted a brass spur gear. The motor is mounted on a hinge so that the gear contacts the recording paper directly.

Pressure-sensitive recording paper is held on a curved aluminum supporting plate. As the motor shaft rotates, the gear teeth scratch lines on the pressure-sensitive paper. On each side of the hinged lid and pivotally mounted to it near the hinge is a spiral-shaped cam made of plywood. The cams serve as a "catch," holding the lid of the apparatus and the record strip at the position of maximum displacement. The motor rotates the gear once per second. The brass spur gear, originally with 30 teeth, has every sixth tooth removed with a file. Thus, with the gear rotating once per second, each tooth inscribes a line on the pressure-sensitive paper every 1/30 second and at intervals of every 1/5 second there is a wider space because of the absence of every sixth tooth.

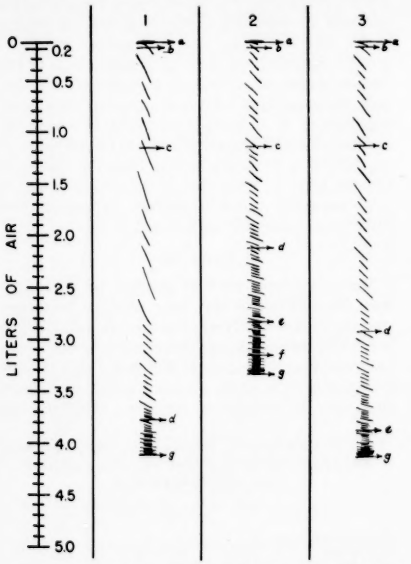

Fig. 2.—Records illustrating method for measuring vital capacity, timed expiratory capacities, and maximum expiratory flow rate (MEFR). Volume calibration scale is on left. Tracings for (1) normal young man, (2) asymptomatic patient with bronchial asthma, (3) same patient 15 minutes after bronchodilator therapy; a = zero volume, b = 200-cc. volume, c=1,200-cc. volume, d=one-second capacity, e= two-second capacity, f = three-second capacity, g = vital capacity. MEFR is computed from time elapsed between b and c (table 1). Values for MEFR in tracings 1, 2, and 3 are 333, 171, and 180 liters per minute respectively.

TABLE 1.—*Maximum Expiratory Flow Rate (MEFR) in Liters per Minute Corresponding to the Number of Lines or Spaces*

Lines*				Spaces†			
No.	MEFR	No.	MEFR	No.	MEFR	No.	MEFR
1	1,800	11½	156	1	300	11½	26
1½	1,190	12	150	1½	198	12	25
2	900	12½	144	2	150	12½	24
2½	720	13	138	2½	120	13	23
3	600	13½	134	3	100	13½	22.3
3½	515	14	128	3½	86	14	21.4
4	450	14½	123	4	75	14½	20.6
4½	402	15	120	4½	67	15	20
5	360	15½	116	5	60	15½	19.3
5½	333	16	112	5½	55.5	16	18.7
6	300	16½	109	6	50	17	17.6
6½	276	17	106	6½	46	18	16.6
7	258	17½	103	7	43	19	15.8
7½	240	18	100	7½	40	20	15
8	225	18½	97	8	37.5	22	13.5
8½	210	19	94.5	8½	35	24	12.5
9	198	19½	92.5	9	33	26	11.5
9½	189	20	90	9½	31.6	28	10.7
10	180	21	85.7	10	30	30	10.0
10½	171	22	81.8	10½	28.5	32	9.3
11	162	23	78.2	11	27	34	8.8

* Interval between two lines = 1/30 second.
† Interval between two wider spaces = 1/5 second.

Calibration of the Apparatus.—After the apparatus has been assembled, it is calibrated as follows. The rubber inlet tube is attached via an adapter and a three-way stopcock to a 50-cc. syringe. The pressure-sensitive paper is placed on the supporting plate. The gear is then placed in contact with the paper, and the motor is turned on at the switch. Approximately 150 cc. of air must be introduced before any displacement of the lid will be observed. Pressure within the rubber bellows is 1.2 cm. H_2O at 1.0 liter displacement and 4.0 cm. at 5.0 liters. The volume displacement is recorded on the paper as a horizontal line for each 50 cc. of air injected. The calibration recorded on the paper is then transferred to a transparent plastic strip and is used for the measurement of vital capacity, timed expiratory capacities, and MEFR.

Test Procedure and Results

Test Procedure.—The operator attaches the pressure-sensitive paper to the supporting plate and places the motor assembly in the position which permits the gear to contact the recording paper. A disposable paperboard mouthpiece is then inserted into the rubber outlet. The test may be conducted with the patient in either the standing or sitting position.

Instruction to the Patient.—The patient is carefully instructed by the operator to inhale as deeply as possible and then exhale as rapidly, as forcefully, and as completely as he can into the mouthpiece. The patient is also told to avoid permitting air to pass through the nose or outside of the mouthpiece. The motor is turned on and the record made.

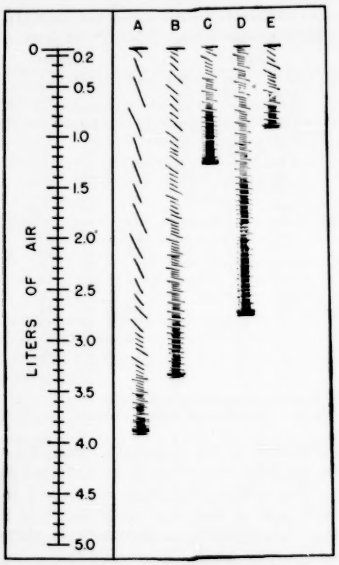

Fig. 3.—Records illustrating pulmonary insufficiency of different etiologies. A, normal young man; *B*, asymptomatic patient with bronchial asthma; *C*, asthmatic patient in paroxysm of moderate severity; *D*, patient with uncomplicated pulmonary emphysema; *E*, patient who had right pneumonectomy.

Computing the Results.—After the patient has completed the forced expiration, the motor is turned off, the record (fig. 2) is removed, and measurements are made as follows: The zero volume line on the plastic ruler is placed so as to superimpose the zero position on the record. The vital capacity of the patient is measured by reading on the plastic calibration strip the volume of the air at the position opposite the furthermost recorded line. The one-second expiratory capacity is obtained by starting at the zero point on the record strip and counting either five wider spaces or 30 lines. The position of this distance on the calibration strip gives the volume of air in liters expired during the first one-second of expiration. The two-second and three-second expiratory capacities are obtained in similar fashion by counting from the zero point to the 10th or the 15th wider space respectively.

As originally defined by Cander and Comroe,[1b] MEFR is determined by measuring the time required for the expiration of the one liter of air from the 200-cc. to the 1,200-cc. volume, as indicated on the calibration strip. This is most readily accomplished by drawing a line across the record at the 200-cc. and 1,200-cc. volumes, counting the number of 1/30-second marks to the nearest half, and then referring to a prepared table of values relating elapsed time to the corresponding MEFR in liters per minute (table 1). When one is measuring the intervals by counting marks, it should be remembered that the wider space occurring every 1/5 second represents an interval of time equal to two smaller spaces or a total of 2/30 second. For records from patients who have marked ventilatory impairment, it is more convenient to count the number of wider spaces and obtain the corresponding MEFR in liters per minute from the space column in table 1. Examples of the measurement of vital capacity, timed expiratory capacities, and MEFR are presented in figure 2.

Comment

Most disorders, whether primary or secondary, that diffusely affect the lung produce important changes in the ability of a patient to exhale forcibly.[2b] The method herein described provides means for measuring the extent to which the time-volume relationship in a single maximal expiration reflects alterations in ventilatory function. Additional information can be obtained from more elaborate ventilatory tests, but their clinical usefulness is hampered by the necessarily complicated apparatus and time-consuming procedure.

Table 2.—*Vital Capacity, Maximum Expiratory Flow Rate (MEFR), and Timed Expiratory Capacities Computed from Tracings in Figure 3*

	Subject				
	A	B	C	D	E
Vital capacity, liters	4.00	3.40	1.35	2.90	1.00
% of Normal*	99	82	52	69	24
MEFR liters per minute	360	138	20	40	..
½-sec. capacity,† liters	2.90	1.22	0.60	0.50	0.70
1-sec. capacity, liters	3.55	2.00	0.85	0.85	0.90
2-sec. capacity, liters	3.87	2.65	1.06	1.40	..
3-sec. capacity, liters	..	3.05	1.20	1.70	..

* Based on height, age, and measured vital capacity of each patient (Baldwin and others: Medicine **27**:243-278 [Sept.] 1948).
† One-half-second expiratory capacity test (Miller and others: Dis. Chest **30**:33-42 [July] 1956).

It is of interest that distinguishable patterns are identifiable in records from patients with ventilatory insufficiencies having different etiologies (fig. 3). In the average normal adult, 70 to 90% of

the vital capacity is accounted for within the first one-second capacity. MEFR in such individuals ranges from 350 to 500 liters of air per minute. During an asymptomatic period in patients with bronchial asthma, the general pattern of the expiratory record grossly resembles the normal tracing; however, when an effective bronchodilator is given, the patient's vital capacity, timed capacities, and MEFR show definite improvement (fig. 2), whereas no consistent changes were observable in this study after similar medication in normal individuals. In this way patients with bronchial asthma having subclinical impairment could be differentiated from normal individuals. In patients having acute paroxysms, the record pattern (fig. 3*C*) shows the vital capacity, timed capacities, and MEFR to be greatly but quite proportionally reduced. In the case of uncomplicated pulmonary emphysema, the vital capacity is reduced but proportionately much less

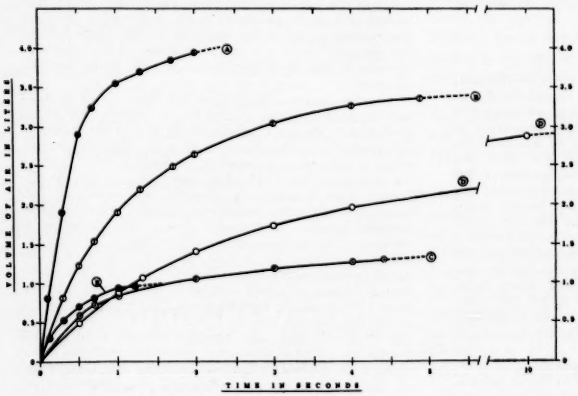

Fig. 4.—Graphic representation of figure 3, illustrating different expiratory tracings of patients with impairment of different etiologies.

so than the markedly reduced time capacities and MEFR (fig. 3*D*). In patients who have had pneumonectomy, the reduction of vital capacity is greater than the reduction of timed capacities and MEFR. The record pattern as shown in figure 3*E* is characteristic of restrictive pulmonary insufficiency. Thus, a patient's expiratory performance may often be appraised with reasonable accuracy by simple inspection of an expiratory tracing (fig. 3).

For precise evaluation of and for estimating small changes in serial comparative studies, accurate computation should be made from the tracings. By plotting the expiratory capacities in liters of air against time in seconds obtained from the records of figure 3, an additional graphic representation of the different expiratory tracings is illustrated in figure 4. The vital capacities, MEFR, and timed expiratory capacities of the tracings in figure 3 are summarized in table 2.

Summary

A simple, inexpensive instrument, capable of measuring vital capacity, timed expiratory capacities, and maximum expiratory flow rate simultaneously and accurately during a single forced expiration may provide permanent records of performance which may be included in a patient's chart for later comparison. The instrument is compact and portable and can be conveniently used in the ward, clinic, or office.

Indianapolis General Hospital, Locke and 10th streets (Dr. Shipley).

Mr. Clifford Wilson provided technical assistance in this study.

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ACUTE MESENTERIC VENOUS THROMBOSIS SIMULATING ACUTE PANCREATITIS

THE VALUE OF PERITONEAL FLUID ANALYSIS

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and
Elias Amador, M.D., Boston

The clinical diagnosis of mesenteric venous thrombosis is often difficult to establish. The following case was incorrectly diagnosed as acute pancreatitis. Several diagnostic peritoneal taps were done during the patient's hospitalization, and in retrospect the gross findings and elevated amylase levels were more suggestive of mesenteric thrombosis than of acute pancreatitis. We hope that this case report will encourage the more widespread use of peritoneal tap as a diagnostic adjunct in cases of obscure abdominal disease.

Report of a Case

At his first admission to the Peter Bent Brigham Hospital, a 63-year-old man had the chief complaint of abdominal pain of two days' duration. Three weeks prior to admission the patient first noted mild constipation, which responded to laxatives and cathartics; three days prior to admission he gradually developed steady periumbilical and lower abdominal pain, which radiated to the middle part of the back. There were occasional cramp-like exacerbations of the pain. One day prior to admission the pain became more severe and was accompanied by vomiting. His last bowel movement, two days before hospitalization, was said to have been brownish-black in color. He had passed no gas per rectum after that. There had been no previous similar episodes of pain, and his general health had always been excellent. He had gained 5 lb. (2.3 kg.) in the past year. During the past several years he had had occasional episodes of postprandial indigestion and periumbilical pain relieved by Alka-Seltzer.

Physical Examination.—On physical examination, his temperature was 97.6 F (36.4 C), pulse rate 110 per minute, respiration 28 per minute, and blood pressure 90/50 mm. Hg. He was a well-developed, obese man obviously in acute distress. His skin was cold and moist, his pulse was rapid and thready, and his respiration was somewhat labored. The heart was slightly enlarged, with normal sinus rhythm and no murmurs; the lungs were clear on percussion and auscultation. Examination of the abdomen showed generalized board-like rigidity with diffuse tenderness and rebound. The tenderness seemed maximal in the right lower quadrant, there was moderate distension, and peristalsis was absent. On rectal examination, the prostate was normal and there was diffuse tenderness in the cul-de-sac but no mass.

Laboratory Studies.—The patient's hematocrit value was 61% on admission, falling to 46% on the second hospital day and 40% on the ninth. The white blood cell count was 27,000 per cubic millimeter, with 88% polymorphonuclear cells; this fell to 13,000 on the second hospital day and to 8,500 on the third. Findings on urinalysis were negative. The serum amylase level was zero Somogyi units on admission; it remained so for three days and then gradually rose to 164 on the sixth hospital day. The peritoneal fluid obtained shortly after admission was reddish-brown in color, with a mild fecal odor. The peritoneal fluid amylase level was 1,690 Somogyi units. No Gram's stain was done. The culture revealed Escherichia cóli. The peritoneal fluid amylase level dropped to 300 on the second hospital day and to 30 on the sixth.

X-ray Reports.—X-ray of the chest showed the lung fields to be clear, and that of the abdomen showed that there was no free air beneath the diaphragm. There were several nondilated, gas-filled loops in the small intestine with fluid levels in the left upper quadrant. There were, in addition, several radiopaque gallstones in the right upper quadrant. The roentgenogram of the abdomen on the fourth hospital day revealed only a minimal amount of gas scattered throughout the small intestine. The left psoas line was obliterated.

Hospital Course.—The patient was brought out of shock with a rapid infusion of 500 cc. of dextran, 900 cc. of plasma, and 500 cc. of whole blood. It was the feeling of the surgeon that the diagnosis of acute hemorrhagic pancreatitis, although not definitely established, best explained the clinical picture. Exploratory laparotomy to rule out perforated ulcer or intestinal infarction was scheduled four hours after admission, but it was cancelled when his blood pressure became unobtainable during the induction of anesthesia. He was then treated with penicillin, streptomycin, and suction with a Levin tube. Therapy with 300 mg. per day of hydrocortisone, given intravenously, was begun on the second hospital day and continued for a week; then the dosage was gradually tapered down. His temperature on the second hospital day rose to 103 F (39.4 C) and spiked to 102 F (39 C) each day thereafter. On the third hospital day he was noted to have some edema and erythema of the flanks, more marked on the left. From the fifth hospital day on, his abdomen became softer and less tender and his general condition appeared slightly improved. On the 10th hospital day he suddenly developed marked difficulty in breathing, and he died while emergency bronchoscopy was being performed. Bronchoscopy revealed that a large, firm, mucus plug had obstructed the glottis.

Postmortem Examination.—The body was that of a well-developed, slightly obese, elderly male, with a distended abdomen. The laryngeal mucosa was slightly swollen and was covered by thick, adherent yellow mucus and by some gastric contents. An abundant amount of tenacious, purulent mucus filled the tracheobronchial tree, the mucosa of which was markedly congested. Each lung weighed 620 Gm., and both were large and firm, with a markedly congested parenchyma which contained numerous small portions of collapsed alveoli. The heart was unremarkable. The peritoneal serosa was covered by a layer of fibrinous exudate, which matted together the intestinal loops. Between these matted loops were loculated cavities which contained a total of 500 cc. of brown, turbid, foul-smelling, fetid fluid. All of the small intestine was dilated, and the serosa had a purple-red color. These changes were most accentuated in a 20-cm. segment of ileum, which was frankly infarcted, with a blue-red wall thickened by hemorrhage. The distal limit of the infarcted segment was 25 cm. proximal to the ileocecal

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valve. The blood vessels of the ascending colon were engorged with blood, but the wall of the whole colon appeared otherwise unremarkable. At the inferior border of the pancreas, the superior and inferior mesenteric veins joined to form a common mesenteric vein. The lumen of this common mesenteric vein was completely occluded by an adherent, gray-red, laminated thrombus. Likewise, all of the superior mesenteric venous tributaries were filled by dark red, firm thrombi. The splenic and portal veins and the mesenteric arteries were free of thrombi. Benzidine-positive liquid fecal matter was found within the stomach and small intestine.

Microscopic Examination.—Microscopic examination of the lung revealed all the lobes acutely congested, with foci of intra-alveolar extravasated erythrocytes in the upper lobes and large portions of collapsed and airless parenchyma in the lower lobes. On examination of the jejunum, moderate numbers of polymorphonuclear leukocytes and engorged blood vessels were seen between the normal-appearing elements of the wall. On the serosal surface there were large masses of neutrophils embedded in meshes of fibrin. Within the subserosal veins recent thrombi were found partially adherent to the intima. Examination of the ileum revealed that the normal cellular detail of the infarcted segment was lost; this was due to necrosis of the wall, which was infiltrated by abundant extravasated blood, bacterial colonies, and foci of cocci. The subserous veins contained recent thrombi, and their walls were infiltrated by neutrophilic leukocytes and scant bacteria. The cecum was unremarkable, except for capillary congestion and thrombosis of the subserous veins. Within the mesenteric vein wall were clumps of histiocytes, monocytes, and polymorphonuclear leukocytes. Attached to the intima was a recent thrombus, whose periphery was being invaded by numerous capillaries. The pancreas and liver were unremarkable, and the remainder of the gross and microscopic examinations was noncontributory.

In summary, the autopsy disclosed extensive thrombosis of the common mesenteric vein and of the trunk and radicles of the superior mesenteric vein. A 20-cm. segment of ileum was necrotic and had produced diffuse peritonitis. There was no evidence of pancreatitis. Since the mesenteric venous thrombosis was not secondary to any abdominal disease process, this case falls within the group described as agnogenic mesenteric venous thrombosis.[1]

Comment

The significant peritoneal fluid findings in this case, which suggest intestinal infarction rather than pancreatitis, are (1) the cloudy, reddish-brown appearance, (2) the mild fecal odor, (3) the positive culture of Esch. coli, and (4) the amylase level of 1,690 Somogyi units.

An unusual feature of this case was the persistently low serum amylase level (zero on three occasions). It has been stated that a serum amylase level of zero is indicative of massive pancreatic necrosis.[2] At autopsy, however, the pancreas was perfectly normal. It is conceivable that the thrombosis of the portal system prevented normal absorption of pancreatic amylase, resulting in the low serum levels.

We are convinced of the value of peritoneal tap in the diagnosis of obscure abdominal conditions. The technique is simple and has not resulted in complications in our personal experience or in the experience of others, as gathered from a review of the literature. We have been using a no. 20 short bevel intravenous or spinal needle in any or all examinations of the mid-lateral quadrant. Neuhof and Cohen,[3] in a series of more than 100 taps, did not observe a single instance of injury to the intestine. Thompson and Brown[4] reported 300 abdominal taps done at Charity Hospital in New Orleans without complication. Moretz and Erickson[5] reported eight instances in which the needle entered the lumen of the small or large intestine in a series of 161 diagnostic taps. In none of these patients could the puncture site in the intestinal wall or evidence of leakage be found on subsequent laparotomy. These workers also did experimental work on needle puncture of the small intestine in dogs.[6] Insertion of a no. 20 needle into dilated loops of small intestine with an intraluminal pressure of 100 mm. Hg resulted in no leakage of gastrointestinal contents after the needle was removed.

It is interesting that they reported an error in diagnosis[6] very similar to that in this case. A patient with a peritoneal fluid amylase level 11.3 times the normal serum amylase content was mistakenly given the diagnosis of pancreatitis. At autopsy, a strangulated gangrenous loop of jejunum was found involved in an internal hernia. The peritoneal fluid, much like that observed in our case, was reddish-brown in color and had a slightly fecal odor. Numerous white blood cells and gram-negative bacilli were seen on a direct smear.

Keith and co-workers[7] have shown that an elevated peritoneal fluid amylase level is helpful in making a diagnosis of acute pancreatitis. The elevation is often more pronounced (averaging 400-1,000 Somogyi units) and lasts two to four days longer in the peritoneal fluid than in the blood. Karlan and Zollinger[8] have noted an elevation of peritoneal fluid amylase level from 800-2,000 units in four out of six cases of mesenteric venous thrombosis in which peritoneal taps were performed. Ellison[9] has stated that, in his personal experience, elevation of the peritoneal fluid amylase level above 1,000 units is strongly suggestive of a necrotic intestine rather than pancreatitis. The mechanism of elevation of peritoneal fluid amylase level with infarcted intestine is presumed to be leakage of intraluminal enzyme through the abnormally permeable intestinal wall.

A Gram stain of the peritoneal fluid is probably the best way to differentiate pancreatitis from infarction of the intestine. In most of the cases of pancreatitis reported in the literature, smear of the peritoneal fluid, although containing many white blood cells, revealed no bacteria. Patients with intestinal infarction characteristically show both white bood cells and gram-negative bacilli on direct smear. Experimental work on dogs by Hill and co-workers[10] revealed that numerous gram-negative bacilli are found on peritoneal fluid smear within four hours of establishing infarction of the intestine.

Summary

Peritoneal tap is a safe and valuable diagnostic maneuver. The gross appearance, odor, and direct Gram-stained smear will serve to differentiate many intra-abdominal diseases. Elevation of peritoneal fluid amylase level above 1,000 Somogyi units, associated with gram-negative bacilli on smear, is strongly suggestive of intestinal infarction.

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ACUTE TUBULAR NECROSIS AFTER TRANSFUSION REACTION DUE TO ANTI-KELL ANTIBODIES

REPORT OF A CASE AND DISCUSSION OF MANAGEMENT

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The pathophysiological alterations in the kidneys of previously healthy individuals who suddenly develop oliguria or anuria have recently been more clearly elucidated. In 1942, Bywaters [1] described the clinical and pathological features of the crush syndrome. Lucke [2] reported that similar ischemic lesions of the tubules could result from several etiological factors and suggested the term lower nephron nephrosis. Oliver,[3] however, demonstrated that the terminal part of the proximal convoluted tubule is involved as often as the distal tubule. Such cases of acute renal failure continue to be described as lower nephron nephrosis, but the syndrome is more appropriately termed acute tubular necrosis.

Numerous etiological factors may produce this syndrome. However, transfusion reactions continue to be one of the most frequent causes. The present report describes a patient who developed acute renal insufficiency after an incompatible blood transfusion due to anti-Kell antibodies but in whom the usual manifestations of a hemolytic reaction were not observed.

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A 37-year-old housewife was referred to Duke Hospital on July 20, 1956, for evaluation and management of anuria of 72 hours' duration. Three days prior to transfer to Duke Hospital she had been admitted to a local hospital for an elective repair of an umbilical hernia and a cystocele and for a diagnostic dilatation and curettage. The hemoglobin level on admission was 11.8 Gm. %. She was given one unit of blood which was considered compatible by the saline cross matching technique. During the third hour of the transfusion, the patient developed chills and urticaria and, one hour after the transfusion was terminated, a temperature of 40 C (104 F), severe vomiting, and diarrhea.

The following morning (July 18), the patient allegedly voided 240 ml. of clear, yellow urine. The vomiting and diarrhea persisted and she received 1,000 ml. of 5% dextrose in water and 1,000 ml. of 5% dextrose in saline solution. As she did not void again, she was catheterized approximately 42 hours after the transfusion. Only 15 ml. of urine was obtained; it was reported to be clear, of yellow color, and completely normal. The nonprotein nitrogen level at that time was 79 mg. %. The icteric index was normal.

On July 19, because of continued vomiting, bloody diarrhea, and fever (38.3 C [100.9 F]), the patient received fluids intravenously, including 1,000 ml. of dextrose in saline solution, 500 ml. of Polysal (a balanced electrolyte solution containing, in milliequivalents per liter: sodium, 140; chloride, 103; carbonate, 55; potassium, 10; calcium, 5; magnesium, 3) in 5% dextrose, and 1,500 ml. of dextrose in water. Parenteral injections of chlorpromazine (Thorazine) hydrochloride, diphenhydramine (Benadryl) hydrochloride,

dimenhydrinate (Dramamine), pyridoxine, and a variety of barbiturates were given. The anuria persisted and the patient was transferred to Duke Hospital.

The history was significant in that the patient previously had received three blood transfusions without reaction, the last being six months prior to this admission, for menorrhagia. She had had five pregnancies without toxemia, edema, hypertension, known albuminuria, or any other indication of renal disease. None of her pregnancies had resulted in erythroblastosis fetalis.

The physical examination revealed a pale, acutely ill patient, lying quietly in bed. She was conscious and cooperative, but complained of severe nausea. The temperature was 37.2 C (99 F), pulse 72 per minute and regular, respiration 16 per minute, and blood pressure 120/80 mm. Hg. Pertinent physical findings included slight periorbital edema; several small ecchymotic areas on the legs and arms; two flame-shaped hemorrhages in the left sclera. The sclerae were not icteric. The neck veins were distended at 45 degrees. The heart and lungs were normal save for an accentuated pulmonic second sound. A moderately tender liver edge was palpable three fingerbreadths below the right costal margin. The spleen was not palpable. The bowel sounds were hyperactive. There was no presacral or ankle edema.

Laboratory Findings.—The laboratory findings were as follows: hemoglobin level, 8.6 Gm. %; hematocrit, 30%; red blood cell count, 3,840,000 per cubic millimeter; reticulocytes, 2.3%; mean corpuscular hemoglobin, 22.3 micromicrograms; mean corpuscular volume, 78.5 cu. μ; white blood cell count, 6,750 per cubic millimeter with a normal differential; platelets adequate. Sedimentation rate, levels of bilirubin, amylase, and total protein, and albumin:globulin ratio were normal. Serologic tests for syphilis were negative. Serum electrolytes (milliequivalents per liter): sodium, 141.3; potassium, 4.0; chloride, 101.2; carbon dioxide, 19.2. Nonprotein nitrogen level was 81 mg. %. Reaction to the Guaiac test was positive; culture was negative for pathogens. The patient was unable to void but was not catheterized. The agglutination tests for typhoid, paratyphoid A and B, and tularemia were negative. The electrocardiogram was normal. Blood cultures were negative.

Diagnosis.—It was apparent on the day of admission that the patient was in acute renal failure, as evidenced by elevation of level of nonprotein nitrogen, acidosis, and complete anuria. There was no evidence to suggest an obstruction or a preexisting renal lesion. The bleeding tendency was thought to be related to acute uremia. The hepatomegaly, neck vein distention, and an accentuated pulmonic second sound suggested early congestive heart failure. The temporal relationship of the blood transfusion and the onset of symptoms was thought significant.

Hospital Course.—The patient remained oliguric for 14 days. In this clinic, a urine output of less than 400 ml. per 24 hours by a patient on a normal diet is defined as oliguria. This is the minimal volume necessary to prevent progressive azotemia. The spleen became palpable on the third day of observation. By the fifth day, the neck vein distention and hepatosplenomegaly had disappeared. The bloody diarrhea subsided on the fourth day. The blood pressure and temperature remained normal during the entire observation.

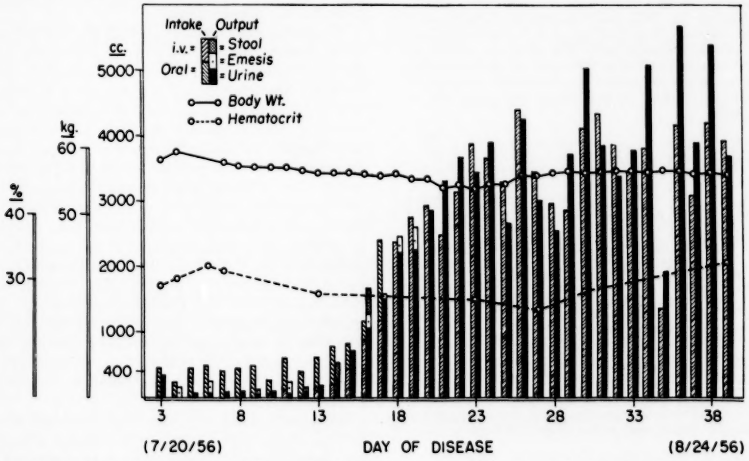

Fig. 1.—Fluid balance, body weight, and hematocrit during oliguric and diuretic period of acute tubular necrosis.

Details of the fluid balance, body weight, and hematocrit are recorded in figure 1. The nonprotein nitrogen level and serum electrolytes, including calcium and phosphorus, are shown in figure 2. Figure 3 lists urine electrolytes in regard to concentration and 24-hour excretion. Arterial pH values on the 11th, 13th, and 16th day of the illness were 7.25, 7.24, and 7.26 respectively. Osmolarity determinations of the plasma and urine were 333.4 and 339 milliosmoles (mOsm.) per liter on the 12th and 329.2 and 325.6 mOsm. per liter on the 16th day of illness. Diuresis began on the 15th day. The electrocardiogram was normal on admission. Electrocardiograms were taken daily and on the eighth day of illness (July 25) changes suggestive of hyperkalemia (peaking of the T waves) appeared. Subjectively, the patient remained fairly cheerful and alert throughout the entire period of observation. Daily vomiting of small volumes for the first 17 days and occasional headaches constituted her only complaints.

Treatment.—The management of this patient was conservative. It consisted of bed rest, administration of antibiotics, respiratory isolation, and administration of 450 ml. daily of 30 to 40% dextrose with insulin (1 unit per 3 Gm.

of dextrose) and 10 mg. of heparin through a femoral catheter passed into the inferior vena cava. Nothing was given by mouth for the first 10 days. No electrolytes were given during this period.

When electrocardiographic changes suggesting hyperkalemia appeared, 10 cc. of calcium gluconate was added to the daily infusion. Testosterone propionate was injected for four days, 50 mg. intramuscularly every six hours. With the onset of diuresis, fluid was given in amounts matching the total output of the previous 24 hours. Oral feeding, at first low in protein and potassium, was begun, reaching a normal diet ad libitum on the fourth day of diuresis. Salt was also allowed ad libitum, and an additional 5 Gm. for two days and 10 Gm. for the third day was given intravenously. Sedatives, previously avoided, were now administered when needed, and multivitamin preparations and ferrous sulfate were added. Strict bed rest was abandoned after the fifth day of diuresis and the patient gradually became ambulant. She was discharged on Aug. 26, 1956, the 38th hospital day.

Follow-up.—The patient returned for checkups on Oct. 3, 1956, and Feb. 22, 1957, and was seen again in October, 1957. She continued to do well, subjectively and objectively, and was clinically asymptomatic. The urine was normal except for low specific gravity. The phenolsulphonphthalein excretion in two hours, which had been 11% on Aug. 10, 1956, and 13% on Aug. 15, was 48% on Oct. 3 and 69% on Feb. 22, 1957.

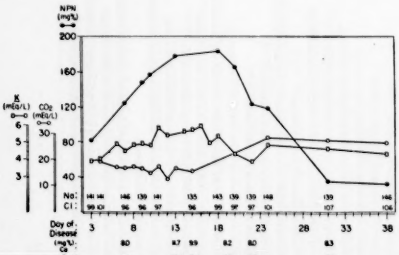

Fig. 2.—Nonprotein nitrogen level and serum electrolytes during oliguric and diuretic period of acute tubular necrosis.

Etiology

The acute renal failure developed immediately after a blood transfusion. Clinically, the patient apparently did not have the common type of hemolytic transfusion reaction; hemoglobinemia, icterus, or hemoglobinuria were not observed. Bloody diarrhea was a prominent feature. A number of other factors in the immediate history and in the presenting condition of the patient could be linked etiologically with an acute renal shutdown, such as bloody diarrhea with high fever, gastroenteritis in the family, and severe abdominal pain as possible indication of an abdominal emergency. The temporal relation to the transfusion, however, was very suspicious. The possibility that the patient might have received blood containing Gram-negative saprophytes, some of which are known to grow in refrigerated blood,[4] was rejected because of the absence of the typical reactions, particularly of profound shock with cutaneous hyperemia.

The diagnosis was obvious when it was found that the patient's red blood cells were Kell negative (kk), that her serum contained extremely potent anti-Kell antibodies, and that a blood sample received from the donor was Kell positive. The donor's cells were strongly agglutinated by the patient's serum when tested by the indirect Coombs' cross matching procedure, but, as is usual with these antibodies, gave a negative reaction when tested by the simple saline cross matching test. A direct Coombs' test of the patient's blood failed to reveal any of the incompatible donor cells in her circulating blood. The blood of the husband and children was also grouped as Kell negative (kk). Therefore, the patient's anti-Kell antibodies were undoubtedly provoked by her previous transfusions and not through her pregnancies.

Excluding the D (Rh_0) factor of the Rh system of blood groups, the Kell (**K**) factor is perhaps one of the most potent of the lesser antigenic blood group factors.[5] Sensitization of a **K**-negative woman by **K**-positive fetus fathered by a **K**-positive man with resulting erythroblastosis fetalis is not uncommon. Sensitization of either **K**-negative men or women by transfusion of **K**-positive blood is relatively frequent after multiple transfusions. Fortunately, only 10% of random white donors are **K**-positive,[5b] thus there is a 9:1 chance of compatibility with the blood of whites (50:1 with Negroes) if the antibody was undetected by the cross match. Unfortunately, the anti-Kell antibody, as in this case, is most often detected only by the Coombs' antiglobulin cross matching procedure. This fact emphasizes the necessity of employing the indirect Coombs' cross matching test for all transfusions, particularly for patients who give a history of previous transfusions or pregnancies.

Inasmuch as no evidence was observed in this patient of the usual rapid intravascular hemolysis any time after the transfusion, it is presumed the incompatible cells were rapidly removed by erythrophagocytosis. The demonstration of extremely potent anti-**K** antibodies in the patient's blood reacting strongly with the donor cells explains fully the pathogenesis of her disease. This case represents another confirmation for the fact that Kell antibodies are of considerable clinical importance as a cause of transfusion reactions. At the time of this patient's hospitalization at Duke Hospital, a former nurse from the same institution died in Tennessee from a transfusion reaction of the same etiology. A description of a case of successful hemodialysis, where Kell antibodies had caused acute renal failure, was published a few days later.[6]

Management

The potential reversibility of the renal lesion of acute tubular necrosis and the possibility of a fatal outcome in case of persistence of the lesion or of mismanagement during the critical period place

an enormous responsibility on the physician in charge of such a patient. Attempts at modifying the lesion directly, such as decapsulation, lumbar block, or adrenal steroid treatment, did not show convincing efficacy and have been abandoned. It became apparent that the tubular cells possess considerable ability to regenerate and regain function if the basement membrane remains intact. It is now generally recognized that the aim of therapy must be to have the patient survive the critical period until spontaneous recovery occurs.

Three principles of therapy are involved: first, to limit the development of biochemical changes as far as possible; second, to anticipate, prevent if possible, and treat, when dangerous, clinical complications directly or indirectly associated with the biochemical changes; and, third, to determine when conservative management threatens to be insufficient and artificial means of reversing potentially fatal biochemical changes should be utilized.

Although excellent discussions of the problems of acute renal failures exist,[7] it seems worthwhile to use the data of this case for a short recapitulation of the main points of conservative management of this condition. Because of the nature of the functional defect, the regulation of water and electrolyte balance and the excretion of the products of protein breakdown are major points for consideration.

Overhydration is the most frequent error in the management of such patients. Throughout the period of oliguria in the hospital, this patient received only an average of 450 ml. of fluid per day, representing a positive water balance of frequently less than 300 ml. per day. This was formerly considered to be insufficient for replacing the insensible losses. However, it is now realized that endogenous sources supply water when protein, fat, or carbohydrate are oxidized and that this water replaces a portion of the insensible loss. In patients with excessive tissue destruction, the catabolism may be so great as to lead to detectable edema on fluid intakes of less than 500 ml. per day.

This patient showed no signs of dehydration. She lost 3.8 kg. (8.4 lb.) during the 12-day period of oliguria, an average of about 0.3 kg. per day. This weight loss results from inadequate caloric intake, which is usually unavoidable and harmless for this period of time. No weight loss in such patients indicates overhydration. Accurate daily weight measurements and physical examination are controls for the state of hydration.

Caloric intake is necessarily inadequate during the period of oliguria. Protein is contraindicated because of potassium and nitrogen. Fat is difficult to administer. The patient is frequently anorexic, nauseated, and vomiting and usually tolerates oral feedings poorly. The parenterally given fat emulsions presently available are not satisfactory. Then, too, most patients have adequate endogenous fat stores to tide them through the period of oliguria. Carbohydrate, therefore, is the main exogenous source of calories. As oral feedings are usually more hazardous and the fluid volume must be restricted, intravenous infusion of 30 to 50% dextrose, fructose, or invert sugar (a mixture of both) is desirable. Such concentrated solutions can be infused into the interior or superior vena cava for a matter of days without producing chemical phlebothrombosis. A polyethylene catheter is passed from the femoral or antecubital vein by a percutaneous technique. Cut-downs or other unnecessary surgery are contraindicated.

The importance of carbohydrates is not primarily to supply calories but to spare protein. Prevention of excessive breakdown of body protein is mandatory, but the protein-sparing effect of nonprotein calories is limited. It has been shown that in healthy fasting subjects 100 Gm. of dextrose per day achieved the maximum protein-sparing effect and prevented ketosis.[8] Considering the stress situation of the severely ill patient, 100 Gm. of dextrose may not be sufficient. Increase in intake of parenterally given carbohydrate must be limited, however, by consideration of the simultaneous increase in fluid intake. The patient discussed in this paper received 140 to 180 Gm. of sugar, representing an average total intake of 624 calories per day for the oliguric period, and did very well.

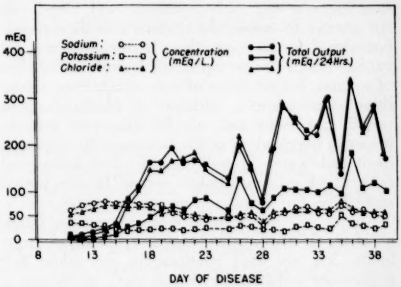

Fig. 3.—Urine electrolytes during oliguric and diuretic period of acute tubular necrosis.

Potassium intake is almost always contraindicated. Without any exogenous supply, potassium originating from endogenous processes, such as tissue breakdown and cation shifts, makes hyperkalemia the most important and most dangerous complication in acute renal failure. The electrocardiogram, not the serum value, is the best guide for determining the clinical danger of hyperkalemia. The patient showed the first electrocardiographic changes suggesting hyperkalemic effect on the eighth day of oliguria. Such minimal changes should be considered serious, and attempts to combat the toxic effects of potassium begun immediate-

ly. The usefulness of calcium and of insulin in hyperkalemia is well established.[9] The efficacy of testosterone or norethandrolone (Nilevar) has never been convincingly proved,[10] but it apparently does no harm if used for a few days; it is not used routinely in this clinic. Cation exchange resins in the form of the sodium salt are available on an experimental basis in most treatment centers for renal diseases. The results in this and other clinics are encouraging, but the resins must be used with caution as hypokalemia may develop. It must be realized that acidosis, hyponatremia, and hypocalcemia aggravate the toxic effects of potassium.

Disturbances of sodium balance, usually iatrogenic, and their management may become a very difficult problem in patients with acute renal failure. Chloride and phosphate are of less immediate concern. The serum phosphorus in this patient rose to a maximum of 14.6 mg. % on the 13th day of oliguria. The significance of phosphate retention lies mainly in its contribution to acidosis.

Acidosis was present in this patient, as was evident from serum carbon dioxide and blood pH. An attempt to correct the acidosis was not seriously considered in this case. The pH deviation was not excessive and the precipitating factor was not loss of sodium, but retention of acid metabolites. Under these circumstances, addition of alkaline salts is usually not useful and may be dangerous because it causes overloading of the intravascular compartment with water through osmotic effect. Extrarenal removal of acid metabolites would be the logical procedure, but it was not necessary in this case.

Antibiotics were administered as a precautionary measure, in addition to respiratory isolation. Antibiotics are not used routinely in this clinic, but respiratory isolation for the patient's protection is considered desirable. The use of a urethral catheter, indwelling or intermittent, should be avoided if possible because of the increased danger of infection.[11]

In this patient the diuretic phase did not offer any problems. The kidneys, of course, were "water-losing kidneys," being unable to concentrate. The nonprotein nitrogen level did not return to normal for two weeks after the diuresis began. This is the usual course. A much longer period of time is necessary for other kidney functions, as for instance phenolsulphonphthalein excretion, to return to normal.[12] Six to 12 months may be necessary for the maximum restoration of tubular function. No difficulties should be encountered in managing the electrolyte and water losses during the diuretic period. The main task is to be aware of them. Excessively massive diuresis indicates overhydration, which can be avoided.

Use of sedatives, analgesics, antibiotics, etc., should be omitted if possible, or the importance of the kidneys for handling the respective compound carefully evaluated. Use of digitalis should be avoided because of the antagonistic effect of potassium; if the serum potassium is reduced by artificial means, the patient may die of digitalis intoxication.

Acute tubular necrosis may be a benign disease. It is so, indeed, in the majority of cases, with proper management. The over-all mortality is assumed to be 20%. Uncomplicated cases of acute tubular necrosis should not be fatal. Problems arise in patients with complicating trauma, infection, labor, or surgery. Conservative management is usually adequate. There remain a number of instances, however, where biochemical changes are too rapid to be compatible with a two-week or more survival of the patient. It cannot always be predicted which patient belongs in this category. In such cases, the availability of an artificial kidney is of immeasurable value.

Summary and Conclusions

Acute tubular necrosis developed after an incompatible blood transfusion due to anti-Kell antibodies in the patient's serum. These antibodies were undoubtedly provoked by one of three previous transfusions. The incompatibility was detectable only by the indirect antiglobulin cross matching procedure.

This near fatal transfusion reaction reemphasizes the absolute necessity of employing the indirect Coombs cross matching procedure in addition to the saline or albumin method for every transfusion and particularly for those patients with a history of previous transfusions or pregnancy. The course of this patient's illness was benign, except for the duration of the period of profound oliguria, which was slightly longer than the average of 11 days. A benign clinical picture while oliguria still persists is no full guarantee for a benign outcome.

The chances for successfully managing acute tubular necrosis by conservative means are excellent in skilled hands. Because of the potential dangers to life which are present during the oliguric period even in the apparently benign case, it is highly desirable to have an artificial kidney available.

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OPACIFICATION OF RADIOLUCENT BILIARY CALCULI

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Biliary calculi are identified radiographically usually as defects in contrast medium–filled biliary structures, less frequently by the density of the calcium content, and occasionally by the presence of gas-containing fissures. Recently, an additional x-ray finding for biliary calculi has been described. Radiolucent biliary calculi were identified by their opacification after prolonged iopanoic acid (Telepaque) administration.[1] The observation of opacification of biliary calculi was made while exploring possible advantages of prolonged iopanoic acid administration in patients whose gallbladders failed to visualize or visualized faintly after the conventional examination with 3 Gm. of iopanoic acid. These patients were placed on a four-day regimen of 3 Gm. of iopanoic acid per day, 1 Gm. after each meal. A relatively fat-free diet was observed during this period. The x-ray examination was made on the morning of the fifth day, with the patient fasting. We have called this prolonged preparation for cholecystography "the four-day Telepaque test." Although an occasional patient complained of diarrhea during this interval, the test was well tolerated.

The opacified biliary stones were characterized radiographically by a generalized rather faint increase in the over-all density of the stones and a sharp increase in the linear density outlining the periphery of the stones. For this reason we have termed this opacification phenomenon "the rim sign" of biliary calculi. Opacification of stones in the gallbladder occurred both in the presence and absence of gallbladder visualization after the four-day iopanoic acid test. Opacification of common duct stones occurred in the absence of common duct visualization.

The incidence of opacifying calculi among all radiolucent biliary calculi could not be determined because the patients examined were a selected group. The opacification of the stones was observed in 3 of 34 patients examined by this method or a slight modification of it. The purpose of this article is to report a case in which the opacification of radiolucent biliary calculi occurred, and the reproduction of this phenomenon in vitro.

From the Division of Radiology (Dr. Salzman) and the Division of Surgery (Drs. Watkins and Rundles), Denver General Hospital and the University of Colorado Medical Center.

Report of a Case

A 79-year-old man was admitted to Denver General Hospital on Aug. 30, 1957, complaining of chills and fever. At a previous admission in 1954, he was found to have diabetes mellitus and adenocarcinoma of the prostate proved by transurethral resection; a bilateral orchiectomy was performed at that time.

On present examination the temperature was 37.5 C (100 F); rales were heard at the base of the right lung; diffuse abdominal tenderness was present; the testes were absent. Laboratory studies revealed a hematocrit of 33%; the white blood cell count was 35,600 per cubic centimeter, with 85% polymorphonuclear cells, 9% stab cells, 5% lymphocytes, and 1% monocytes. Urine was negative for sugar and acetone but loaded with pus and bacteria. Chest x-ray was within normal limits. The patient was given 2

units of blood, tetracycline (Achromycin), and supportive treatment, with improvement. On Sept. 13, the patient appeared jaundiced. The total bilirubin level was 7.4 mg. per 100 cc. The jaundice gradually subsided during the following week.

A plain x-ray of the abdomen on Sept. 16 failed to reveal any opaque biliary calculi (fig. 1*A*). A cholecystogram on Sept. 25, after the patient had been given 3 Gm. of iopanoic acid, showed only a faint visualization of the gallbladder (fig. 1*B*). A repeat cholecystogram after the patient had received 3 Gm. of iopanoic acid per day for four days revealed opacification of numerous large, irregularly shaped calculi in the distal right and left hepatic, common hepatic, and common bile ducts to the ampulla of Vater. The gallbladder was faintly visualized and major biliary ducts were not visualized (fig. 1*C*). On Oct. 16 a film of the abdomen showed that opacification of the radiolucent biliary calculi had disappeared. The gallbladder was still faintly visualized (fig. 1*D*). A repeat cholecystogram on Oct. 19, after another regimen of 3 Gm. of iopanoic acid per day for four days, revealed reopacification of the bile duct stones and faint visualization of the gallbladder (fig. 1*E*). A plain film of the abdomen taken Nov. 14 showed disappearance of the radiolucent bile duct stones and the gallbladder (fig. 1*F*).

On Oct. 26, a scrotal abscess appeared which was incised and found to communicate with the urethra. A cystostomy was done on Oct. 30. The patient's course was complicated by bronchopneumonia, and he died Nov. 28, 1957. The significant autopsy findings were bronchopneumonia, healed pyelonephritis, biliary cirrhosis, chronic cholecystitis, cholelithiasis, and choledocholithiasis. There were numerous large, soft, earthy stones dark brown in color filling the distal hepatic, common hepatic, and common bile ducts to the ampulla of Vater, as was seen on the clinical x-ray examinations. These bile duct stones were packed tightly in the region of the cystic duct and partially obstructing the cystic duct, which may explain the faint visualization of the gallbladder at cholecystography. The gallbladder con-

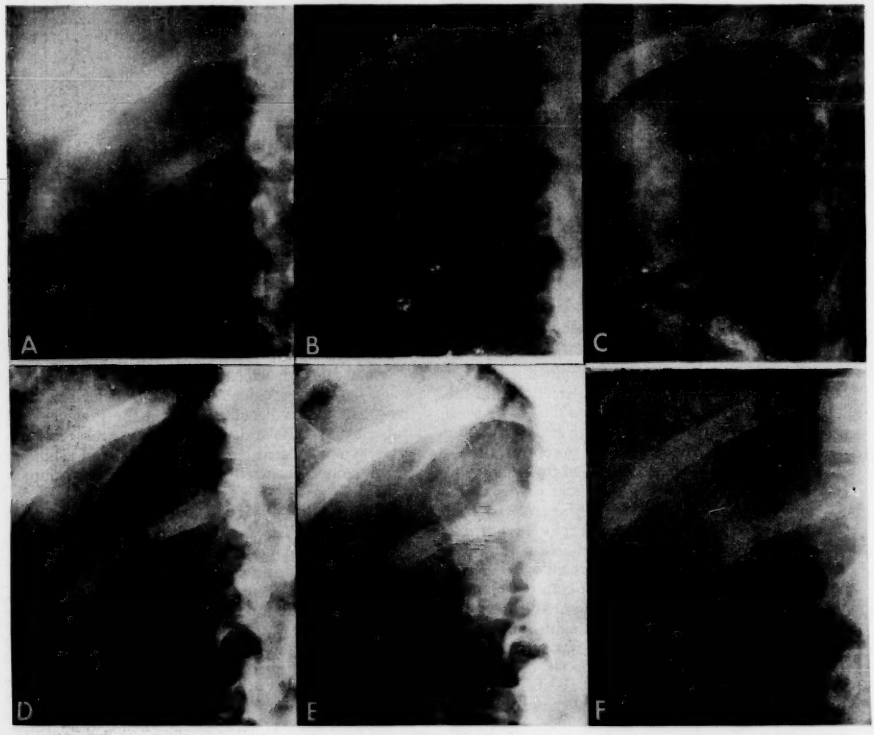

Fig. 1.—*A*, preliminary x-ray of abdomen showing no opaque biliary calculi. *B*, after 3 Gm. of iopanoic acid, faint visualization of gallbladder, residual iopanoic acid in colon. *C*, after four-day iopanoic acid test, large irregular stones fill distal right and left hepatic, common hepatic, and common bile ducts; faint visualization of gallbladder. *D*, two weeks after four-day test, disappearance of opacification of bile duct stones; gallbladder still faintly visualized. *E*, after repeat four-day test, bile duct stones opacified again; faint visualization of gallbladder. *F*, three weeks after repeat test, disappearance of opacification of bile duct stones and gallbladder.

tained thin yellow fluid and numerous stones of a different character from those found in the major bile ducts. The gallstones were small, oval, hard, and deeply pigmented.

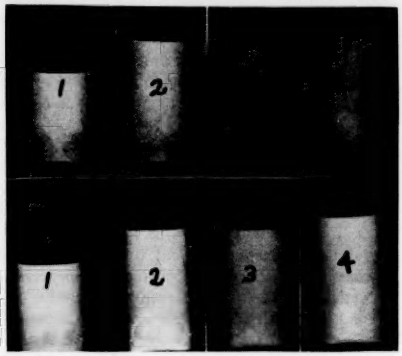

Fig. 2.—In vitro studies. *Top*, immediate x-ray. 1, gallstones in iopanoic acid bile. 2, common duct stones in iopanoic acid bile. 3, gallstones in normal bile. 4, bile duct stones in normal bile. *Bottom*, after three days at room temperature. Only bile duct stones in iopanoic acid bile show increased opacification.

In Vitro Studies

The opacification of the radiolucent bile duct stones and the failure of the radiolucent gallstones to opacify clinically were reproduced in vitro. Samples of gallstones and bile duct stones obtained at autopsy were immersed in plastic tubes of iopanoic acid bile and normal bile. The iopanoic acid bile was obtained at laparotomy from the gallbladder of a patient who had received 3 Gm. of iopanoic acid the evening prior to the operation. The normal bile was obtained at autopsy from a normal gallbladder. The tubes were x-rayed immediately (fig. 2, *top*), kept at room temperature, and x-rayed again four days later (fig. 2, *bottom*). The bile duct stones in the tube of iopanoic acid bile were strikingly opacified and there was no additional opacification of the bile duct stones in the normal bile or of the gallstones in the iopanoic acid bile and normal bile. This corresponded to the observations made on the clinical x-ray examinations of the patient. This evidence supports the idea that the opacification of radiolucent biliary calculi is the result of a deposition of iopanoic acid or an iodinated product of iopanoic acid on the surface of the stone. Furthermore, the failure of the gallstones to opacify and the opacification of the bile duct stones indicate the opacifying quality is inherent within the stone and not the result of instability of the colloidal system of the iopanoic acid bile. Work is in progress to determine the substance in some biliary calculi which is responsible for the opacifying quality.

Summary

The four-day iopanoic acid (Telepaque) test is a prolonged preparation for cholecystography for opacification of radiolucent biliary calculi. In vitro studies showed that opacification is a result of a deposition of iopanoic acid or an iodinated product on the surface of the stones. The opacifying quality is inherent in the stone and is not due to an instability of the colloidal system of the bile.

West Sixth Avenue and Cherokee Street (4) (Dr. Salzman).

The iopanoic acid used in this study was supplied as Telepaque by Winthrop-Stearns, Inc., New York.

References

1. Salzman, E., and Warden, M. R.: Telepaque Opacification of Radiolucent Biliary Calculi: "The Rim Sign," Radiology, to be published.

ANTIBIOTICS AFTER APPENDECTOMY.—We have also noted a serious complication from the use of antibiotics, namely postoperative pseudomembraneous enterocolitis. There has been increasing evidence in the past 18 months that some of the appendiceal deaths could be attributed to acute pseudomembranous enterocolitis occurring postoperatively. Most of the cases have occurred in middle aged or elderly individuals. Antibiotics, sometimes of the broad-spectrum type, were given following operation. During the postoperative period, usually between the sixth and tenth day, these patients experienced a rather sudden onset of crampy abdominal pain, abdominal distention, fever, chills and diarrhea. Within a short time they went into profound and unremitting shock in the terminal stage. The picture has been frequently confused with severe diffuse peritonitis or rupture of a hollow viscus. The passage of many watery, greenish stools has been a frequent, but by no means, invariable finding. Tremendous amounts of fluids are lost into the gastrointestinal tract and this probably accounts for the severe shock and dehydration. Micrococcus pyogenes may almost invariably be cultured in the diarrheic stool in the severe cases.—F. A. Bothe, M.D., Appendectomy, *The Surgical Clinics of North America*, December, 1957.

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MUMPS IMMUNIZATION

Edward B. Shaw, M.D.

MUMPS is a very rare infection during the first few months of life even when there is intimate exposure. The resistance of the infant is probably not due to transplacentally acquired antibodies, for, unlike the situation which obtains in measles, protective antibodies against mumps do not long persist in the serum of those who have had the disease. Gamma globulin prepared from plasma gathered from the population at large is completely without value against the risk of this infection. Only the gamma globulin prepared from plasma of those who have been hyperimmunized against mumps virus has any probable protective effect. This effect is at best unpredictable and not completely reliable.

There is no satisfactory method for protection against mumps after exposure. Susceptibility may be determined by means of the skin test with material prepared from the virus which is grown on embryonated eggs. The tuberculin reaction–like positive response is supposed to indicate the probability of previous infection and immunity. Negative tests are inconclusive, and the presence of egg protein may lead to false-positive results.

Some degree of passive immunity against mumps may be conferred by the use of hyperimmune gamma globulin, which is commercially available. It is impossible to evaluate adequately this protection. The communicability of mumps is relatively low; about one-third of the adult population is said to be immune because of previous undiagnosed and perhaps subclinical infection. Apparently successful protection may simply be the result of residual immunity in the subject or of insufficient exposure. Failures of protection are not infrequently encountered when susceptibility is accompanied with intimate exposure.

Active immunity against mumps may be induced by two injections of the commercially available vaccine which has been cultured on embryonated eggs. This immunity cannot be induced in the interval between exposure and the appearance of disease, so that it does not provide the greatest potential usefulness for a method of active immunization. Such active immunization, although it does not appear quickly enough to protect from known exposure, is of such short duration that it cannot be of great value to the susceptible adult who may be exposed to the disease from time to time unless immunization is repeated at least annually. Unfortunately, many adults react somewhat violently to the injections of the vaccine.

Children who are exposed to mumps should be allowed to develop the disease—but obviously very little can be done to prevent this should one choose to do so. There is much less likelihood of infection after mumps exposure than is the case with measles or chickenpox. Probably the low order of communicability accounts for the fact that so many adults escape the disease during childhood only to develop it in later years. Orchitis and oophoritis rarely develop before puberty, and the other complications of mumps which may occur in childhood, including meningitis, are not usually of great severity.

Deliberate exposure to the disease in childhood is another matter. This may be desirable for the child as the only means of inducing lifelong immunity, but it introduces the potential risk of secondarily exposing adults who may then have the illness with greater severity and sometimes with permanent sequelae. It is desirable that the child acquire this infection before puberty as the best source of permanent immunity and the prevention of the disease during adult years, at which time serious complications are more frequently encountered. The exact protective effect of methods of artificially induced active or passive immunization are difficult to evaluate and are certainly not completely reliable.

Clinical Professor of Pediatrics, University of California School of Medicine, and Chief, Communicable Disease Department, Children's Hospital, San Francisco.

ORGANIZATION SECTION

PUBLIC RELATIONS INSTITUTE IN CHICAGO—AUGUST 27-28

The A. M. A.'s 1958 PR Institute at the Drake Hotel in Chicago, Aug. 27-28, billed as the "V. I. P. Meeting," is designed for physicians, medical society staff personnel, and others working in the medical public relations field. The workshop-styled program will get down to PR practicalities at its opening session with a discussion of medicine in a changing world. From the lead-off "What Do You Know?" session, the meeting will move into deliberations on "What Have You Got To Say?" "How Do You Say It?" "Who Do You Know?" and "Are They Listening?" Top people in related fields, including communications and human relations, will take part in the program.

REPORT PUBLISHED ON HILL-BURTON PROGRAM

The results of a two-year study of the Hill-Burton Hospital Survey and Construction Program will be available in booklet form Aug. 1, from the Committee on Medical and Related Facilities of the A. M. A. Council on Medical Service. Sections in the report include introduction, summary, conclusions, recommendations, federal grants-in-aid, background and basic administration, general hospitals, tuberculosis hospitals, public health centers, mental, chronic disease, and nursing home facilities, diagnostic or treatment centers, rehabilitation facilities, and other reference material. In addition to reviewing the legislative background of the act and much other data, reports are included on field surveys made in Arkansas, California, Connecticut, Georgia, Illinois, Iowa, Kentucky, Maryland, Michigan, Mississippi, Montana, New Jersey, Oregon, and Washington. A limited number of copies will be available to individual physicians and medical societies.

NEW FILM ON FOOD QUACKERY

How "medicine men" dupe the public into spending millions of dollars on unnecessary or overpriced nutritional products is shown in a new American Medical Association film. Prepared for airing over local television stations under the auspices of local medical societies, this 27-minute film, "The Medicine Man," dramatically pinpoints the fight against quackery in the food and nutrition field.

The film singles out problems which stem from health lecturers who travel from town to town giving misinformation on nutrition as a tie-in to plugging their products of questionable merit and from door-to-door salesmen who misrepresent the value of nutritional products. The film also shows how the medical profession cooperates with the Food and Drug Administration and voluntary agencies such as the National Better Business Bureau in the crackdown on these food quacks.

First showing of the film will be at the A. M. A. Public Relations Institute, Aug. 27-28, at the Drake Hotel, Chicago. Prints will be available to local medical societies after Sept. 15 from the A. M. A. television film library.

RENEWAL OF ILLINOIS LICENSES

Most physicians living outside of Illinois and holding an Illinois license to practice may not be aware that all licenses expired automatically on June 30 under a new law which went into effect on July 1.

The last legislature passed a law requiring re-registration by July 1 in every even numbered year beginning with 1958. Because the Department of Registration and Education had only the addresses in effect at the time the original licenses were issued, and not subsequent changes, it has been able to notify only a small percentage of licensees, both in and out of the state.

Physicians desiring to renew their licenses in Illinois should write to the Department of Registration and Education, Capitol Building, Springfield, Ill., giving name, address, and license number and sending $6, the biennial re-registration fee. The biennial re-registration measure had the backing of the Illinois State Medical Society because it will provide a current published list of those entitled to practice medicine and make a check possible on those operating unlawfully.

WORK ABSENCE GUIDE TO BE PUBLISHED

The A. M. A. Committee on Medical Care for Industrial Workers (a joint committee of the Councils on Medical Service and Industrial Health) is currently working on a "Guide for Measuring Work Absence Due to Illness and Injury." To obtain additional data for such a booklet, the Committee will publish a "preliminary guide" which will be used in field surveys and will be mailed on about Aug. 1 to companies, individuals interested in the subject, and medical societies. Medical societies may send information on their activities in this area to the Committee.

COUNCIL ON NATIONAL DEFENSE

The following two papers were presented at the Sixth National Medical Civil Defense Conference in San Francisco on June 21, 1958. This annual conference is sponsored by the A. M. A. Council on National Defense.

The Hon. Leo A. Hoegh was appointed by President Eisenhower on June 24 as the director of the new Office of Defense and Civilian Mobilization. Prior to that, he served as administrator of the Federal Civil Defense Administration for 11 months.

The Hon. R. Walter Riehlman, of Syracuse, N. Y., is the second ranking minority member of the House Committee on Government Operations and a member of its military operations subcommittee which conducted extensive hearings on civil defense for national survival in 1956. As a result of these hearings, a number of important recommendations were made to strengthen and improve the national civil defense program.

The role and leadership of the federal government to civil defense determines, to a large measure, the activities of state and local governments. These two papers are being published as a matter of interest to the medical profession because they outline the current thinking and efforts of the executive and legislative branches of the federal government in the field of civil defense.

FRANK W. BARTON, *Secretary.*

CURRENT CONCEPTS OF THE FCDA

Leo A. Hoegh, B.A., J.D., Washington, D. C.

I know of no group that is more receptive to civil defense, no group that is more responsive to our planning, and no group with more significance to the ultimate survival of this nation, than the members of the American Medical Association. We appreciate your splendid cooperation and performance.

Medical Care

We proposed, some time ago, that the responsibility for health and medical care of the surviving population be delegated to the Public Health Service of the Department of Health, Education, and Welfare. We want to delegate this whole responsibility to the PHS, and, along with it, the responsibility for writing the medical portion of the National Civil Defense Plan which we have drawn and which I will discuss more fully later.

At no time did we consider doing this without first bringing it before the A. M. A. The latest opportunity for full discussion came in a meeting, late in April, of the Civil Defense Committee, the chairman of which is Dr. Lueth. This was a fine meeting. Dr. Lueth himself called it a "most worthwhile and productive type of conference." I know it was most helpful to me. Dr. Blasingame, General Manager of the A. M. A., wrote to me to say:

> It is my pleasure to advise you that by action of the Board of Trustees at a meeting on May 30, 1958, the Association concurs in the principle of the proposed delegation—provided that it is specified that the states, local political subdivisions thereof, and other organizations and agencies concerned with the health of the population surviving an enemy attack on the United States will be afforded an opportunity to participate actively in and otherwise contribute to the planning, preparation, and implementation of the contemplated nationwide health and medical care program designed to utilize nonfederal facilities and resources.

Of course we would not want it any other way, and both the Public Health Service and FCDA have so assured the Civil Defense Committee and, as a consequence, the A. M. A. itself. As soon as possible after July 1, formal negotiations will be opened with the Secretary of Health, Education, and Welfare, concerning this proposed new delegation.

It is essential that all physicians and all medical facilities be counted as part of this nation's civil defense because when you look squarely at it, civil defense to be effective will involve every human being, professional or nonprofessional, and every facility that can be found. How we go about this is, of course, the real subject of the contract FCDA made with the A. M. A. nearly a year ago. Under this contract, the A. M. A. will study, develop, and recommend the planning, training, and operational organization needed as a basis for a national emergency care plan for treatment and care of casualties and noncasualties prior to, during, and after an attack.

The A. M. A. Commission on National Emergency Medical Care is directing this study—using the Minneapolis-St. Paul area as an example—so that the A. M. A. can come up with recommendations covering (1) the use of professional and nonprofessional personnel of the medical and related

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Administrator, Federal Civil Defense Administration.

Read before the Sixth Annual National Medical Civil Defense Conference, San Francisco, June 21, 1958.

professions preattack and immediately postattack; (2) the functions and responsibilities of the medical profession that may be delegated and performed by paramedical personnel; (3) the training and education that is needed by all health personnel, professional and nonprofessional, for wartime operational capability, and the sorting of casualties.

We expect quite a bit, don't we, for our $150,000? This, however, is only a part of our expenditures that should interest you. You will be glad to know that we are back in the MEND program—Medical Education for National Defense. We are going to put $135,000 next year, on equal shares with the Army, Navy, and Air Force, in this program to acquaint instructors with medical problems anticipated in time of national disaster so that graduates are better prepared to assume the responsibilities of military or civil emergency medicine.

Radiologic Defense

Now, in this concept of keeping civil defense functions within those areas best equipped to deal with them, there are certain "holes" that we feel it is our responsibility to plug. There is, for instance, no normal civil agency equipped or trained to deal with the problem of radiation monitoring. Therefore, we have instituted our own program for radiologic defense. It should be of special interest to you because it is critical to the survival of the maximum number of people.

There literally is no place in the whole United States that can consider itself immune to radioactive fall-out caused by nuclear weapons. Every individual must know where there is invisible danger and where there is comparative safety. This can be determined only if we build true radiation monitoring capability throughout the entire country. We are building it. We have undertaken a program that has two parallel actions: We are multiplying our training course—at national headquarters and in the regions—and we are concentrating on science teachers who in turn can teach many others how to use the variety of instruments necessary for scientific measurement.

Simultaneously, we are delivering sets of radiologic instruments and instructor kits to the high schools of the nation. Six thousand schools will have the instruments in time for school opening in September, and another 9,000 will get them in time for the second semester. This will equip half of the high schools in this school year, and by June, 1959, over one million students will be properly trained. All high schools will be furnished the equipment and instructor manuals by 1960.

We are furnishing radiologic devices to the states and target cities. Through their civil defense personnel, it is expected that over 100,000 city and state employees in police, fire, and other departments will be properly trained during the next year. The federal network of fixed monitor stations will use the facilities of all federal agencies. Instruments are being distributed to 221 Weather Bureau stations and to 600 Civil Aeronautics Administration stations. Also included are 79 Air Weather Service monitoring points under the Department of Defense. By the end of 1958, the federal network will have available about 900 monitoring points over the nation, operating on a round-the-clock basis.

We feel certain that through these actions we will build the monitoring capability that we must have. It is possible that fall-out resulting from an attack on this country could claim twice as many lives as blast and heat.

Shelter Policy

But knowing where intense radiation exists is of little value if we are not prepared to protect ourselves against it. This is one of the reasons for the recent announcement of a national shelter policy which will give us for the first time a logical and workable approach to this phase of civil defense. Under this policy, the administration will undertake the following five courses of action:

1. Inform every American of the possible effects of nuclear attack and of the actions he and state and local governments can take to minimize them. Every American must know the hazard and how to meet it.

2. Make sampling surveys of existing structures, particularly in larger cities, to determine shelter capabilities. Many facilities already afford some fall-out protection. We must get this information.

3. Accelerate research to show how shelter may best be incorporated in both existing and new structures and to improve shelter designs.

4. Construct a limited number of prototype shelters for varied geographical and climatic areas. They will have practical peacetime uses, such as underground parking garages, school and hospital cafeterias, subways, highway fills, and homes.

5. Incorporate fall-out shelters in appropriate new federal buildings that will be constructed from now on. Federal example is an indispensable stimulation to state and local government and private investment for the same protective construction.

In essence what we have here is a do-it-yourself shelter program with strong federal leadership, guidance, and example. Through this we can simultaneously accomplish three things: 1. We can create protection at compartively low cost. 2. We can help to insure that all fall-out shelter is so arranged that the areas have a daily common use while remaining available for emergency. 3. We can avoid the tremendous tax burden that would be laid on the nation if a massive federally financed shelter construction program were undertaken.

Incidentally, as individuals and home owners, you might like to know that FCDA currently is

distributing a new, plain-language, illustrated publication showing how to create fall-out shelter in a dwelling at comparatively low cost.

National Plan

The fact that every person in the United States could be affected by fall-out is the best reason I know why everyone, without exception, must consider himself a part of civil defense. Civil defense, I am sure you know, is no special force or magic device. Properly, it is a combination of all nonmilitary actions that can be taken to protect our nation and our people.

These actions cannot be at random or without direction. They must be planned in advance and executed according to predetermined patterns. Hence we have completed the National Civil Defense Plan after many months of intensive work by many people and with the guidance and assistance of many groups and organizations. The plan has been coordinated with federal government agencies and with state and local governments as well. You have made a valuable contribution in its preparation.

It sets forth the specific mission of each level of government and, for that matter, of the individual citizen. In this one document are all of the basic civil defense principles and responsibilities for protecting life and property. It creates a civil defense channel of coordination down which instructions will be transmitted and up which requests for assistance will be made. It states our mission clearly —"To protect life and property from the effects of attack by preparing for and by carrying out emergency functions to prevent, minimize, and repair injury and damage." It then sets forth the functions and, step by step, how the mission is to be accomplished, and by whom.

Detailed explanations for special services have been or will be drafted as annexes to the plan. One of these annexes—the Medical and Health Plan—will become the obligation of the Public Health Service by delegation to the Department of Health, Education, and Welfare.

This National Plan can become fully effective only if the Senate approves a House-passed measure, the Durham Bill (H. R. 7576), which is now in one of its committees. The plan is keyed to the principle that the federal government has the responsibility for the over-all direction and coordination of civil defense action—something only hinted at under existing law.

Civil defense must be taken seriously today by every level of government and by every citizen. Certainly civil defense is taken with utmost seriousness in Russia, according to dispatches from Russia just last week. The United Press said that every Soviet citizen is being required, this year, to take a 22-hour training course, with a wider and more detailed study program to follow.

The newspaper *Soviet Patriot* revealed that DOSAAF—the Voluntary Society for Assistance to the Army, Air Force, and Navy—has set itself the prime task of instructing the entire population in antiaircraft, antiatomic, antichemical, and antibacteriological defense. It also said that within the next two years, civil defense units will be established in every factory, collective farm, school, university, and other institutions throughout Russia. Looks like they are copying our plans. They are doing by compulsion what we hope to accomplish through persuasion and guidance, but our way is the best way. When the American people are told of the threat and how to meet it, and when they have leadership by government, they will respond.

We do not anticipate or expect war. We simply recognize that as long as city-destroying weapons exist, we must prepare against them. The enemy, in desperation or sheer idiocy, could push the wrong button. Therefore, we will continue to add to the very substantial progress we already have made in federal guidance and federal actions. I am thinking now of certain functions which only government can perform—such things as warning, communications and control, survival planning, and recovery, all backed up by research and education.

I will not go into the technicalities of all of them here, because I want to devote my remaining time to the all-important question of control. I do this particularly because in the Civil Defense Committee meeting of which I spoke earlier, there seemed to be some concern about martial law and military assumption of civil defense responsibilities. The questions arose out of a misunderstood military address to our state civil defense directors.

There is no question today of the military's role in relation to civilians. Very quickly it is this: The military is to be prepared to support the civil efforts if its mission permits. In other words, the primary role would be military; but if they are in a position to do so, then they have to be prepared to support the civil effort. We do not expect that the military will ever take over.

We are doing everything possible to strengthen government's capacity to operate in an emergency through our Continuity of Government Program. We say that it is necessary to retain this local government. So our primary objective is to see that the civil government is so strengthened that no "martial law" will become necessary.

Control is critical to survival. Government at all levels must be able to continue operating and directing in any emergency. Four elements are necessary to insure this: First, lines of succession for key government personnel must be established. second, alternate sites for conducting government must be chosen, fully equipped, and kept in full operating condition. Third, there must be duplication and

safe storage of those records essential to continued government operation and for the protection of individual rights. Fourth, provision must be made for the full use of all government resources—personnel, facilities, and equipment.

Plans are well under way for discharging these control and communications responsibilities at the federal level. Some states and cities also are moving in concert, but of course much more needs to be done, as it does in all areas of our responsibilities. At the same time, we must reach every individual with the guidance that may mean the difference between living and dying. This is one of our greatest challenges, but one we must not fail to meet, because despite everything I have said here, civil defense first, and most importantly, is acutely personal. Individuals might have to depend upon their own knowledge and resourcefulness for days or weeks after a major attack. There are five simple steps to safety—that everyone must know: (1) warning signals and what they mean, (2) your community plan for emergency action, (3) protection from radioactive fall-out, (4) first aid and home emergency preparedness, and (5) use of Conelrad—640 or 1,240 for official directions.

I realize that many of our citizens expect a civil defense to be built somewhere and shipped out to them, complete, and functioning. There are even more, perhaps, who would be willing to buy civil defense, just as they buy military defense with their tax dollars. They miss the point that since nuclear war would affect everyone, there would be no one to employ. Civil defense is everyone's business.

No, we can't buy civil defense, we must live it. There is no other way. All we can do is to make people understand this, see to it that the hardware is in place, and give the people the leadership and the know-how they must have in time of crisis. When governments are prepared and capable of leading, I am convinced the people will rally to their support—only then will we have effective civil defense. This is a challenge to all of us but especially to government. We will—we must—meet it.

THE CONGRESSIONAL PROGRAM FOR CIVIL DEFENSE

R. Walter Riehlman, Washington, D. C.

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Very briefly, I shall summarize recent congressional action affecting civil defense and outline in general terms the civil defense legislation now pending in Congress, together with a few comments on what I consider the essential elements of a workable civil defense program for our nation.

First, however, I should like to congratulate the American Medical Association, and particularly the Council on National Defense, for its fine work in civil defense. The continuing support of the Association, as well as the support of the medical profession in general, has contributed significantly to the civil defense work of our subcommittee on military operations, and I am sure its support has been of immeasurable help to the Federal Civil Defense Administration.

Your presence at this conference today evidences the personal interest of you gentlemen of the medical profession, and I commend you for that interest. No single group in our society can perform a greater civil defense service than can the medical profession.

In time of emergency, your skills and energy will be essential to the saving of many lives. Virtually the entire recovery effort will center around and be dependent on the vital task of the medical profession.

Almost equally important is the civil defense service which can be performed by the medical profession before an enemy strikes. As leaders in your local communities, you gentlemen significantly influence public opinion. People respect your judgment and tend to follow the example you set, particularly with respect to civic and community affairs. Your attitudes toward civil defense and other public affairs mean a great deal in crystallizing public opinion. Your personal interest in and concern with civil defense will have much to do with the general attitude the public takes toward this very important subject.

In this connection, permit me to give a special word of praise for one of your distinguished colleagues and a close friend of mine, Dr. Fred Hiss, of Syracuse, N. Y. In addition to being the protector of my good health, Dr. Fred Hiss is actually my mentor in the ways of civil defense. On my visits to him he may forget to tell me how much I owe, but never does he forget to preach civil defense. And gentlemen, he knows the ins and outs of it, believe me. My visits may stretch out way beyond the appointed time, but the knowledge I gain is invaluable. An outstanding physician and a wonderful person to know, this gentleman is fully aware of his responsibilities as a civic and community leader and represents the best traditions of the medical profession in every respect.

I should also like to pay my respects to Federal Civil Defense Administrator Leo Hoegh. Last month the House military operations subcommittee,

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U. S. Congressman, 35th Congressional District, Syracuse, N. Y., second ranking minority member of House Committee on Government Operations and member of its Military Operations Subcommittee.

Read before the Sixth Annual National Medical Civil Defense Conference, San Francisco, June 21, 1958.

of which I am the ranking minority member and former chairman, had the privilege of interrogating Governor Hoegh regarding civil defense policies and programs of the federal government. His sincerity of purpose was most impressive, and I believe I can say on behalf of the subcommittee that the determination with which he has undertaken his task as FCDA administrator is encouraging to us all.

As some of you may know, our subcommittee on military operations has done a great deal of work in the field of civil defense. I am aware that sometimes we have been referred to as the chief critics of the FCDA, but I prefer to consider our relationship with the FCDA as more of a partnership arrangement. I am sure Governor Hoegh agrees with me in this respect, and I want to thank him personally for his many kind remarks about the work of our subcommittee.

The most recent civil defense work of our subcommittee was in connection with President Eisenhower's reorganization plan no. 1 of 1958, which was transmitted to Congress on April 24th of this year. Under the provisions of this plan, the Federal Civil Defense Administration and the Office of Defense Mobilization will be merged to form a new agency called the Office of Defense and Civilian Mobilization. The new agency will be located in the Executive Office of the President.

This reorganization represents a significant development in civil defense at the federal level. In my view, it deals with one of the three principal requirements of civil defense at the federal level today. Briefly summarized, these requirements are (1) a federal organization which has the prestige and status required to deal effectively with other federal agencies and with state and local governments and which is capable of planning and executing a realistic national program for civil defense; (2) federal authority to provide financial assistance to the states and localities for certain administrative and personal expenses; and (3) a federal program to assist the states in developing protective measures against nuclear weapons effects.

Federal Organization

Before speaking of the second and third requirements, let us consider for a moment this very important matter of federal organization. The question of how best to organize for civil defense has been a matter of study in the federal government for more than a decade. The President's plan did not spring forth in full bloom. Rather, it was the culmination of long study and planning extending back to the end of World War II.

Until 1949, responsibility for civil defense planning was carried out by the War Department and the Department of Defense, whose main concern in the matter was to identify the types of programs needed to preserve the industrial mobilization base in the event of a future war. In 1949, civil defense planning responsibilities were vested in the National Security Resources Board, which had been created by the National Security Act of 1947. It was concerned with a wide range of nonmilitary defense matters, including economic stabilization, resource allocation, and defense production. This board, the NSRB, developed a general plan for civil defense, and in late 1950—after the beginning of hostilities in Korea—two actions were taken to establish a functioning civil defense program.

Almost simultaneously, a Federal Civil Defense Administration was established by executive order, and legislation providing for a statutory agency of the same name was submitted to Congress. That legislation became the Federal Civil Defense Act of 1950, sometimes called Public Law 920 of the 81st Congress.

This emergency legislation provided the framework for an operating civil defense program, but experience has demonstrated that the task assigned to the operating agency—the FCDA—was too limited in scope. In effect, major nonmilitary defense planning was left as a function of the NSRB, while the FCDA was given the task of establishing the operating program of civil defense. The remaining functions of the NSRB later were vested in the Office of Defense Mobilization, which has operated as a part of the President's Executive Office.

This division of nonmilitary defense functions between ODM and FCDA has continued until the present time. It has been the cause of much confusion and no doubt has hindered the development of an effective program. The President's plan will go a long way toward eliminating this source of confusion. For the first time, we will have a single source of policy guidance at the highest level of the federal government. In my opinion, this is one of the most important developments in civil defense since World War II.

For years we have been trying to establish a workable framework for civil defense in the federal government. And this transition to the new Office of Defense and Civilian Mobilization is the latest step in a long and arduous effort to move out of the planning stage and into a functioning program. This has been a prime objective of the military operations subcommittee from the inception of our civil defense studies. Nearly four years ago, while chairman of the subcommittee, I prepared a concurrent resolution which would permit the transfer of FCDA to the Department of Defense. The FCDA would thereby become a fourth department coequal with the three military departments.

My purpose was to break the log-jam then besetting the civil defense program. I was convinced of the need to move out of the planning stage and into an operating civil defense program. And the close relationship between civil defense and active military defense indicated to me that civil defense should be virtually an adjunct of our military program. That measure, which was introduced the next year as H. Con. Res. 108, sought to avoid the many

side-issues and confusing relationships existing in civil defense by placing unmistakable authority in an operating agency with great prestige and with basically similar duties.

This resolution, together with other measures introduced in the House, was the basis of the comprehensive and exhaustive civil defense investigation undertaken by the subcommittee under the chairmanship of Congressman Chet Holifield of the state of California. Subsequently, at the conclusion of our investigation, I introduced a new bill (H. R. 2239) designed to revamp our entire civil defense effort and place the program in a separate Cabinet-level Department of Civil Defense. The bill also would authorize basic new civil defense functions, including the construction of shelters and vastly increased federal assistance to state and local civil defense programs.

One other essential feature of the bill is that the civil defense functions of the ODM would be transferred to the new Department of Civil Defense. In this respect, of course, my bill and the President's reorganization plan are in basic agreement. In either case, complete responsibility for federal civil defense policy would be vested in a single agency of high standing in the federal government.

Now, the President's plan will accomplish this organizational objective, but it does not change the basic authority underlying the federal civil defense program. Reorganization plans are by nature limited to organizational changes. New functions can be added only through new legislation.

Federal Assistance for State and Local Programs

This brings us to the second and third requirements. In addition to improved organization, the federal civil defense effort must include substantially increased support for state and local civil defense programs. I am aware of the current debate over whether the federal government is performing too many functions which might better be performed by the states. Without going into the issues of that debate, I can only say this: The states and localities have not been able to develop the level of civil defense preparedness required; and, whether we like it or not, such preparedness can be achieved only if the federal government assumes a major role both in terms of leadership and in financing.

I am convinced that the FCDA should be authorized to provide financial assistance to states and localities for civil defense personnel and administrative expenses and should be authorized to assist in developing positive protection against nuclear weapons effects, including shelter protection against blast and radioactive fall-out. The bill which I introduced (H. R. 2239) would authorize both of these functions within the framework of a comprehensive national master plan for civil defense. Legislation sponsored by the FCDA would also authorize a part of these functions but only on a much more limited scale.

The FCDA-sponsored legislation (H. R. 7576) passed the House unanimously and is now pending before the Armed Services Committee of the Senate. This bill would authorize federal contributions for state and local civil defense personnel and administrative expenses, and it would authorize the FCDA to donate and maintain radiologic detection instruments.

These are two very important functions, and both are badly needed. But they will not, by themselves, do the total job required in civil defense today. One of the major additional requirements is a federal shelter construction program. Because of the nature of modern weapons, shelter construction, together with radiologic detection equipment, is a vital factor in assuring the survival of our population.

Protective Measures Against Nuclear Weapons

One of the first things we need to do is to get radiologic detection devices into the hands of a large number of people throughout the United States. These people should be thoroughly trained in the use of such devices. Today, only a small percentage of our population has any conception of how to use radiologic monitoring and detection equipment. The nature of the threat requires that we have possibly 100 million such devices in use. Virtually the entire population should participate.

Once we develop this type of capability, once we are able to measure and monitor redioactive fallout, then we can make maximum use of existing structures to shield ourselves from the deadly effects of fall-out. Simultaneously, we should begin the construction of shelters specifically designed for fall-out protection and a reasonable degree of blast protection. Obviously, we cannot expect to do this job overnight, but we should get started without further delay.

At the recent hearings of our subcommittee on military operations, the technical experts of FCDA advised us that enough test data have been developed to enable us to start constructing civil defense shelters immediately. Naturally, further improvements and refinements in shelter designs and construction techniques will be forthcoming, but we cannot wait for absolute perfection. Such improvements can be incorporated as we go. The important matter is that we have the required technical data, and we know the job that needs to be done.

Governor Hoegh has mentioned (see this issue, page 1748) the national shelter policy which he announced at our recent hearings. This national shelter policy represents an important step toward more effective civil defense in the United States. While some of us may disagree as to the specific measures required and how we should go about obtaining the shelter protection we need, there is no debate over the basic requirement itself.

It is my understanding that, under the new national policy, a survey of existing structures will be made to obtain definite information on the capa-

bilities of these structures to provide fall-out shelter. Even now, certain buildings, mines, subways, and tunnels afford some fall-out protection. Designs of shelters will be perfected to assure the most economical and effective types. A number of prototype shelters suitable to different geographical and Climatic areas will be constructed and tested by actual occupancy for realistic periods of time.

Several key personnel of the Naval Radiological Defense Laboratory remained in a shelter at the Nevada Proving Ground during an actual test shot this past year. To my mind, this is ample proof of their confidence in the shelter designs that have been developed. The prototype structures to be built under the new shelter policy may be in underground parking garages, schools, hospitals, industrial plants, and residences and apartments. And, of course, it should be observed that these facilities will also have practical peacetime uses.

I share the opinion of most members of Congress that in programs like this the government should lead the way and set a good example. Therefore, it is gratifying to know that, hereafter, plans for future government buildings, be they large or small, will contain facilities for shelter.

H. R. 7576, the bill now pending in the Senate, does not deal with the shelter program, but it will have a bearing on the success of the new shelter policy as well as on any other shelter policy that might be adopted in the future. In view of the closely related requirement for a substantial radiologic monitoring and detection capability, the authority contained in H. R. 7576 is extremely important.

If the FCDA can proceed to purchase and distribute to the states radiologic monitoring equipment, we can begin to build the type of monitoring program required. In the future, such a program could be expanded so that eventually the entire population might develop a monitoring and detection capability.

Support for FCDA Program

One additional matter I wish to discuss with you this morning is the problem that FCDA has had in obtaining congressional support for its program. This problem is directly reflected in congressional action on FCDA appropriations requests. Since its beginning in 1951, FCDA has asked for a total of 2 billion dollars to set up and operate its vast program. Only about 450 million dollars has been appropriated by Congress for this entire period. In other words, FCDA has been forced to struggle along with less than 25% of the money it believed necessary to successfully launch and operate this very important program. This 450 million dollars spent for civil defense during the past eight years amounts to approximately 1% of the 40 billion dollars spent each year on our military defense.

I have no quarrel with the spending of this money for military defense. I am wholeheartedly in favor of a strong military program. My objection is that so little has been appropriated for the other phase of our defense effort, the civil defense phase. Now, I do think the situation is beginning to improve. This year FCDA was granted substantially the amount of funds it requested, and there are signs that the future will see even greater improvement.

In the past, one of the roadblocks in the way of full congressional support for civil defense was the lack of a realistic over-all National Civil Defense Plan. I must confess that we in Congress have at times been critical of the seeming laxity of FCDA in not presenting to us something definite to indicate just where we are headed in civil defense. Actually, this problem is closely tied in with the requirement for improved organization at the federal level.

If the impending reorganization results in the development of a realistic and comprehensive program, then I'm sure the Congress will be willing to increase its support for the agency and the program. I think it is basically as simpe as that. Congress has not been inclined to support civil defense in the absence of a realistic national program. Once we achieve a civil defense organization with the status and capacity required to develop such a program and once such a program is presented to Congress, then I think we will see a different attitude on the part of Congress.

This is not to imply that the present agency has not sincerely attempted to do the job, and I do not wish to leave that impression. In my opinion, they simply have not had the authority, the status, and the tools that they need. I recognize that there is no single answer to the complex and changing problems of civil defense. I have endeavored to indicate my own views, with particular reference to pending legislation, including the President's reorganization plan.

Summary and Conclusions

In summary, the reorganization plan holds promise of much improved nonmilitary defense organization at the federal level, with the elimination of confusion and duplication in policy direction. H. R. 7576 will, to a limited extent, increase the federal role in support of state and local civil defense programs. And the recently announced National Shelter Policy constitutes a recognition of the fundamental shelter requirement in civil defense. Taken together, these measures represent a substantial step in the right direction, although they fall short of the total program I have supported in proposed legislation. Despite my own misgivings, however, I sincerely believe that we ought to do everything we can to support this start toward a more realistic civil defense program.

There are many other aspects of civil defense deserving attention at this time, but I shall mention only one more. That is the extremely important matter of health and medical considerations under the new federal organization. Throughout our entire civil defense study and investigation the subcommittee's effort to achieve a stronger federal program has been staunchly supported by the American Medical Association. The Association has endorsed my bill (H. R. 2239), and it has followed every development with great interest. In connection with our consideration of the President's reorganization plan, the Association submitted a lucid statement pointing up the importance of the medical and health aspects of civil defense. I should like to include the following excerpt from that statement:

> The basic concept of national mobilization is accepted as the "will of the people to resist." This concept depends on the sustained physical and mental health of the people and as such has interested the American Medical Association for many years.
>
> In its concern with the health and medical aspects of civil defense, the Association has recognized, for a number of years, the urgent need for federal leadership, direction, and coordination. The Association believes that civil defense, like military defense, is an integral part of national defense which requires greater federal responsibility and leadership.
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> More specifically, the Association is concerned with the status, in any federal agency, of the office responsible for medical and health activities. The Association is convinced that medical and health activities are one of the most, if not the most, important function in sustaining the "will of the people to resist."

I can only echo these sentiments and say that our subcommittee is also concerned with the status of health and medical activities in the new Office of Defense and Civilian Mobilization. We know of the vital importance of these activities in any civil defense program. I wish to commend the Association for this strong statement in support of our civil defense work, and I assure you that our subcommittee will continue its efforts to secure a realistic civil defense program for our country.

COUNCIL ON MEDICAL SERVICE

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STUDY OF PERINATAL MORTALITY AND MORBIDITY PROGRAMS IN THE UNITED STATES

PART 5

EARLY NEONATAL MORTALITY STUDY IN DELAWARE

The Committee on Maternal and Infant Mortality was established in 1937 by the Delaware State Medical Society at the request of the Delaware State Board of Health. It was composed of one member from each county of the state and was directed to work with the state board of health "in an effort to abolish as soon as feasible the present system of midwifery in Delaware."

With the cooperation of the state board of health, the committee began a study of maternal deaths in 1937. The questionnaire method was used, and each death was classified as to cause and preventability. A review of infant deaths was included in the committee's work in 1943. At this time the infant death cases were not reviewed individually but only to the extent that information was available from the health department.

Beginning in 1955, the infant deaths studied have been limited to those occurring in the hebdomadal period (the first seven days after birth). Data are obtained on each individual case by reviewing the hospital charts and in some cases by interviewing the physicians concerned. This work is done by members of the committee or by other physicians at the committee's request.

The membership of the committee has increased to eight and now includes four pediatricians, two general practitioners, and two obstetricians, with one of the obstetricians serving as chairman. The two previous chairmen served seven and three years. Members are retained on the committee if willing to serve; geographical representation is adhered to by the president in his appointment of new members.

Scope of Study

The purpose of this study is to account for deaths which occur during the first seven days of life. Objective analyses of the various phases of obstetric and pediatric management of these cases is expected to reveal the preventable factors, if any, in these deaths and thereby to lead to a lowering of the neonatal mortality rate. The committee

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This is the fifth and last of a series of articles prepared by the Committee on Maternal and Child Care of the Council on Medical Service on perinatal mortality and morbidity study programs that are being conducted in various parts of the United States.

Committee members are: W. L. Crawford, M.D., Chairman, Rockford, Ill.; R. B. Chrisman Jr., M.D., Coral Gables, Fla.; Philip S. Barba, M.D., Philadelphia; Harold S. Morgan, M.D., Lincoln, Neb.; Garland D. Murphy, M.D., El Dorado, Ark.; Howard A. Nelson, M.D., Greenwood, Miss.; J. L. Reichert, M.D., Chicago; Donald A. Dukelow, M.D., Consultant, Chicago; Philip F. Williams, M.D., Consultant, Bala Cynwyd, Pa.; Edwin J. Holman, Consultant, Chicago; and Mr. George W. Cooley, Secretary, and Mr. Donald B. Berg, Research Assistant, Chicago.

also studies the maternal deaths that occur in Delaware, but as these are becoming very few (three in 1956), this phase of the program is incidental to the main study. (The committee is striving to reduce this number to zero, however.)

Method of Operation

Case-Finding.—During the early part of each year the state board of health furnishes to the committee the identifying information on each maternal death and each hebdomadal infant death which occurred in Delaware during the previous year. The information supplied includes the name and address, the date of death, the cause as indicated on the death certificate, and the name of the hospital.

Collection and Processing of Data.—The chairman and members of the committee and other physicians designated by the committee in the various hospitals of the state review the hospital charts and other records to determine race, period of gestation, age at death, autopsy results, cause of death, contributing factors in the infant, and contributing maternal factors. These physicians evaluate each case as objectively as possible and classify it as preventable, possibly preventable, or nonpreventable. Each preventable and possibly preventable case is further classified as previable premature (500-999 Gm.), viable premature (1,000-2,500 Gm.), or full-term (more than 2,500 Gm.). (Since some "previable" infants live, deaths of fetuses in this weight range are classified as possibly preventable whenever preventable factors are discovered.) A brief summary is made for each of these cases, including the cause of death and the preventable factors.

Follow-up and Use of Findings.—Statistics are compiled indicating the total number of live births, the number of hebdomadal deaths, the hebdomadal death rate, the number of deaths in the first 24 hours and the rate of such deaths per 1,000 live births, and the proportion of premature (previable and viable) and full-term infants in each of these classifications. An annual report in the *Delaware State Medical Journal* lists these statistics, as well as the causes of death, for each of the 10 Delaware hospitals giving maternity care. The report also provides summary data on each death considered preventable or possibly preventable and discusses other important aspects of these cases.

The need for more and better autopsies is emphasized in these reports. It is pointed out that the exact cause of death can be determined only by composite analysis of the baby's and mother's clinical courses, by laboratory studies, and by postmortem examination of the baby. The percentage of cases for which the cause of death remained undetermined was almost inversely proportional to each hospital's autopsy percentage. It is pointed out that such categories as prematurity and atelectasis should not be given as the primary causes of death, since autopsy usually reveals a more specific cause. Correctible conditions are discussed frankly, and each report contains recommendations for improvement of the study.

No direct follow-up of individual preventable factors has been made, as anonymity in the study is considered essential.

Results

During 1943, the first year that infant deaths were considered in the committee's review, the rate was 43.3 per 1,000 live births. By 1956 it had been reduced to 21.9. In the 15 year period from 1940 to 1955 the early neonatal death rate dropped from 23.9 to 14.4. In 1955 the rate ranged from 10.6 to 22.2 among the individual hospitals. Although the numbers of live births in these hospitals are too small to give statistical significance to one year's figures (the range was from 159 to 2,831), it is believed that the steady decrease in the rates in several of the hospitals over a period of years indicates a great deal of improvement in care. The autopsy rate was 45.8% for all hospitals, with the largest hospital having a rate of 74.4%.

Of the 10,569 live births in 1955, 152 resulted in death within the first seven days of life. Four of these deaths occurred at home, and of the hospital deaths, 51 (34.3%) were classified as previable premature, 61 (41.3%) as viable premature, and 36 (24.3%) as full-term.

Of the 152 early neonatal deaths, 15 (9.8%) had preventable factors. This percentage is not large, but it does indicate the need for continued studies of this type to discover what deficiencies still may be present in the care of these newborn infants. Four of the 15 (one viable premature and three full-term) were classified as preventable and 11 (two previable, seven viable premature, and two full-term) as possibly preventable.

Comments and Conclusions

The members of the Committee on Maternal and Infant Mortality have studied early neonatal deaths occurring in Delaware in some detail for the past two years. They believe that improvements can be made, but they feel that there has been much progress even though the study has been conducted more or less informally. They do recommend, however, that each hospital set up a committee, including representatives from the departments of pediatrics, obstetrics, anesthesiology, and pathology, and that these committees study each neonatal death within a month after it occurs. The committee believes that a more accurate statistical analysis could be made at the end of each year if some more frequent and uniform method of receiving and reviewing cases could be established.

MEDICAL NEWS

FLORIDA

State Medical Election.—The Florida Medical Association has installed the following officers: Dr. Jere W. Annis, Lakeland, president; Dr. Ralph W. Jack, Miami, president-elect; Dr. Samuel C. Harvard, Brooksville, first vice-president; Dr. Walter E. Murphree, Gainesville, second vice-president (re-elected); Dr. Joseph W. Douglas, Pensacola, third vice-president; Dr. Samuel M. Day Jr., Jacksonville, secretary-treasurer (reelected); and Dr. Shaler A. Richardson, Jacksonville, editor (reelected).

Miami Researchers Win Award.—Dr. Robert J. Boucek, associate professor of cardiology, University of Miami School of Medicine, Coral Gables, has received the major award of 300 pounds sterling in the Ciba international competition for studies related to aging. His paper, honored among 62 projects submitted by research workers in 19 different countries, was on "The Effect of Tissue Age and Sex upon the Metabolism of Rat Collagen." Dr. Boucek's co-workers were Nancy L. Noble, Ph.D., J. Frederick Woessner Jr., Ph.D., Kung-Ying Tang Kao, Ph.D., and Harry R. Elden, Ph.D. The research was financed by the Howard Hughes Medical Institute. Other awards in this competition were given to research workers in Tanganyika, London, Minneapolis, Los Angeles, Prague, Geissen (Germany), Bern, and Maebashi City (Japan).

ILLINOIS

Chicago

Dr. Huggins Honored.—The Charles Mickle fellowship for the year 1958 has been awarded by the University of Toronto to Dr. Charles B. Huggins, director, Ben May Laboratory for Cancer Research, University of Chicago, for his "contributions in the field of cancer." The award is made to that member of the medical profession and related sciences who is considered by the Council of the Faculty of Medicine of the University of Toronto "to have done most during the preceding 10 years to advance sound knowledge of a practical kind in medical art or science." The fellowship is accompanied by an award of $1,000.

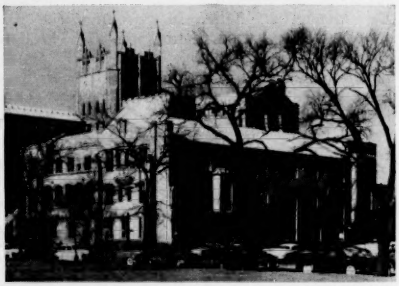
Society News.—The Chicago Society of Industrial Medicine and Surgery has elected the following officers: Drs. Walter J. Phillips, president; George J. Cooper, vice-president; Bille B. Jennan, secretary; and Charles M. Drueck, treasurer.——The Chicago Ophthalmological Society has elected the following officers: Dr. J. Vernal Cassady (South Bend, Ind.), president; Dr. Clifford P. Sullivan, president-elect; Dr. Manuel L. Stillerman, vice-president; Dr. Joseph S. Haas, secretary-treasurer; Dr. Theodore N. Zekman, councilor; and Dr. David E. Shoch, recording secretary.——The following officers have been elected to the Chicago Orthopaedic Society for 1958-1959: president, Dr. Carlo S. Scuderi; vice-president, Dr. John H. Moe; president-elect, Dr. Newton C. Mead (Evanston); secretary, Dr. William A. Larmon; and treasurer, Dr. Charles V. Heck.

Dr. Clark Appointed Chairman of Department of Surgery.—Dr. Dwight E. Clark has been appointed chairman of the department of surgery of the University of Chicago, effective July 1, succeeding Dr. Lester R. Dragstedt, who becomes emeritus next year, but resigned from the chairmanship to complete research he is conducting. Dr. Clark was an intern, resident, and instructor in the University Clinics of the the University of Chicago, 1937-44, when he became chief of surgery and commanding officer of the Army Medical Corps's Oak Ridge, Tenn., hospital. He returned to the university in 1947 as associate professor of surgery and in 1951 was appointed professor and senior attending surgeon of Billings Hospital, and secretary of the department. Dr. Clark is vice-president of the Society of Nuclear Medicine and a member of the board of governors of the American College of Surgeons.

Pavilion for Infant and Maternal Research.—Dedication of a new research laboratory, a one-million-dollar remodeling of the former Mother's Aid Pavilion and now named the Mother's Aid Research Pavilion of the Lying-In Hospital of the University of Chicago Clinics, was held June 13. Two of the three floors have a series of laboratories including equipment for radioactive materials: the third floor will be used for steroid hormone studies; the second floor has laboratories for investigations in pathology, cytology, microbiology, and biochemistry. Facilities for parent education classes, exercise rooms, and elements important in obstetrical practice are on the second floor. One of the hospital's outpatient clinics and various offices are on the first floor. Appointments to the Lying-In staff for the

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

research program include Dr. Kimball C. Atwood, of the Oak Ridge Laboratories, who becomes associate professor of medical genetics, effective Sept. 1. The research program in cytology is under Dr. George L. Wied. Research into causes of infant deaths is under Dr. Edith L. Potter. A scientific program was held June 14 which included as speakers Dr. Duncan E. Reid, Boston; Dr. George W. Corner, New York City; Dr. Nicholson J. Eastman, Baltimore; and Donald H. Barron, Ph.D., New Haven, Conn.



Mother's Aid Research Pavilion, Lying-In Hospital, University of Chicago Clinics.

LOUISIANA

Study of Tropical Diseases.—The Louisiana State University School of Medicine, New Orleans, has sent eight teachers from American and Canadian medical schools to Latin America for training in tropical diseases. Following two days of orientation in New Orleans, the teachers proceeded to the tropics for eight weeks of observation of diseases and health programs. Five went to Costa Rica, Panama, El Salvador, and Guatemala; the other three went to Puerto Rico, the Dominican Republic, and Haiti. The program is made possible by the voluntary cooperation of medical and public health leaders in the respective countries, the Overseas Missions of the U. S. State Department, and the Pan American Sanitary Bureau of the World Health Organization. This is the last group to receive such fellowships under a grant of $120,000 to the university from the China Medical Board of New York, the primary interest of which is medical education in the Far East and in the U. S. The program has been in operation for three years, during which time 69 fellowships have been awarded to teachers from 53 medical schools. Louisiana State University has received approval of a grant from the National Institute of Allergy and Infectious Diseases to continue this program for five more years on a broadened basis to include teachers and graduate students from nonmedical institutions.

MICHIGAN

Skin Bank to Aid Treatment of Burns.—A living "skin bank" has been established in the surgery department of the University of Michigan Medical Center, Ann Arbor. Reserved for the treatment of serious burns, the bank contains narrow strips of human skin 12-thousandths of an inch thick. These are stored in a nutrient fluid at controlled temperatures to provide "homografts" in emergencies. The homograft used at the Medical Center is taken from the donor's back, just below the shoulders. Dr. Irving Feller, instructor in surgery, has charge of the skin bank. The homografts in the skin bank are being obtained, with the permission of relatives, from persons who have just died.

Tuberculosis in Michigan.—The Michigan Tuberculosis Association has reported that chest x-ray surveys of the Michigan Department of Health in 1957 were nearly twice as effective as in previous years in finding suspected cases of tuberculosis. A total of 8,059 tuberculous suspects were found among the 399,364 films taken. This was a rate of 20.2 suspects for every 1,000 x-rays. In the preceding five years, the rate ranged from 10 to 12. An increasing portion of the newly reported tuberculosis cases are being found through selective x-ray surveys. A total of 5,011 cases of tuberculosis were reported last year in Michigan. This is a reduction of 9% from 1956. In recent years new cases of tuberculosis have fluctuated between 5,000 and 6,000, showing an over-all gradual decline. In the first four months of 1958, there were 491 more new cases reported than during the first four months of 1957.

Personal.—Dr. Harry E. Carnes, a member of the clinical investigation staff, Parke, Davis & Company, has been appointed director of medical correspondence and editor of *Therapeutic Notes*, published monthly in five languages for physicians throughout the world. Dr. Carnes will assist as consultant in the medical education and training of the sales staff, and assist the hospital medical service staff. ——Dr. Gordon B. Myers, chairman, department of medicine, Wayne State University College of Medicine, Detroit, has been appointed head of the new university service in internal medicine at Harper Hospital. With the addition of Harper Hospital, Wayne now directs three services in internal medicine, the others at Receiving Hospital.——Dr. Elwood A. Sharp, of Grosse Pointe, medical assistant to the president of Parke, Davis & Company, has been elected an affiliate of the Royal Society of Medicine.——Dr. John R. McDonald, head of a section of surgical pathology in the Mayo Clinic and professor of pathology in the Mayo Foundation,

Graduate School, University of Minnesota, Rochester, became director of pathology at the Harper Hospital in Detroit, July 1.

MINNESOTA

Clinic Lectures.—Dr. Geoffrey Watkinson, of the University of Leeds, England, gave a lecture on "Secretory Studies in Uncomplicated Peptic Ulcer, Hematemesis and Achlorhydria by the Use of 24-Hour Gastric Analysis" at the Mayo Clinic, Rochester, May 12. On May 14 he lectured on "Steroid Therapy in Ulcerative Colitis."—Dr. Nanna C. Svartz, head of the King Gustav V Research Institute and professor of medicine in the Caroline Institute in Stockholm, Sweden, spoke on "Isolation of the Rheumatoid Factor" at the Mayo Clinic, Rochester, May 21.

NEW YORK

Fellowships for Research at Rochester.—The University of Rochester has established a program of postdoctoral fellowships to be awarded graduates of approved medical schools to enable them to pursue research in the School of Medicine and Dentistry. The Buswell fellowships are made possible by the bequest of the late Mr. Ralph Hochstetter and are intended to assist "well qualified" doctors of medicine to prepare adequately for academic careers. Buswell Junior Fellowships will be awarded to medical graduates who have completed at least one year of internship or equivalent training. Research experience is not required. Junior fellows are expected to spend about 90% of their time in research or in advanced study in preparation for research. Fellowships will provide a basic stipend of $4,500 to $6,000 per year, and may be renewed with increments for a second or third year; $350 per year may be provided for each dependent. Buswell Senior Fellowships will be awarded to medical graduates who have held a Buswell Junior Fellowship for two or three years or have had comparable experience. Senior fellowships will provide a basic stipend of $5,500 to $8,000 per year, with provision for annual increments; $350 per year may be provided for each dependent. Applications will be received at any time. Information may be obtained from Dr. Lawrence E. Young, Chairman, Committee on Buswell Fellowships, University of Rochester Medical Center, 260 Crittenden Blvd., Rochester 20. N. Y.

New York City

Rappleye Scholarship Fund.—After 27 years as dean, Columbia University College of Physicians and Surgeons, Dr. Willard C. Rappleye has retired, and the alumni and teaching staff have decided to mark this occasion by setting up a special scholarship fund in his name. This will be a capital fund, the income of which will be used each year to assist needy students. Contributions may be sent to the Committee for the Willard Cole Rappleye Scholarship Fund, Room 3-424, 630 W. 168th St., New York 32.

Appoint Director of Department of Medicine.—Dr. Kenneth R. Crispell has been appointed professor and director of the department of medicine at New York Medical College, Flower and Fifth Avenue Hospitals. Dr. Crispell comes to New York from the University of Virginia Medical Center, Charlottesville, where he was associate professor of internal medicine. He will succeed Dr. Linn J. Boyd, who resigned from this post after 30 years to become director of the expanded division of graduate studies. Dr. Crispell was a fellow in internal medicine at the Ochsner Clinic in New Orleans, and a fellow in biophysics at Tulane University. He went to the University of Virginia as a Commonwealth Fellow in 1949. He became assistant professor in internal medicine in 1951, and associate professor in 1955.

PENNSYLVANIA

Philadelphia

Dr. Grice Comes to Philadelphia from Harvard.—Dr. David S. Grice, assistant clinical professor of orthopedic surgery, Harvard University, Boston, has been appointed chairman of the University of Pennsylvania School of Medicine's department of orthopedic surgery, effective Sept. 1. Dr. Grice will succeed Dr. Paul C. Colonna, who will retire following 16 years as chairman of that department.

Medical History Lectures.—Dr. George Rosen, Columbia University Faculty of Medicine, will give the first annual Victor Robinson Lecture in History of Medicine at Temple University School of Medicine Sept. 23, 4 p. m., in the medical school auditorium, on "Victor Robinson—A Romantic Medical Historian." This lectureship is named in honor of Dr. Robinson, professor of history of medicine at Temple University from 1929 until his death in 1947.

Society News.—The Philadelphia Academy of Surgery has elected the following officers: Adolph A. Walkling, president; W. Emory Burnett and J. Montgomery Deaver, vice-presidents; William T. Fitts, secretary; Stephen D. Weeder, treasurer; and Jonathan E. Rhoads, chairman, Committee on Scientific Business.—The following officers of the Philadelphia Roentgen Ray Society have been elected for the year 1958-1959: president, Dr. Herman W. Ostrum; vice-president, Dr. John T. Brackin Jr. (Abington); secretary, Dr. Roderick L. Tondreau; treasurer, Dr. Randal A. Boyer; and counselor-at-large, Dr. Harold J. Isard.

Woman's College Plans Research Wing.—The Woman's Medical College of Pennsylvania has announced plans for a new 2-million-dollar wing to be constructed starting next fall at the northeast end of the present college building. Principally designed for research, the wing will consist of six stories and a basement. In the over-all plans, some diagnostic and treatment facilities are also included. A grant of $500,000 from the U. S. Public Health Service has been given to the college for laboratories, which with a matching amount already secured, will provide the research floor. The college is still soliciting funds to complete its 2-million-dollar goal needed to include the teaching and diagnostic facilities. The addition of the new wing with the expanded department of physiological chemistry reportedly will enable the college to take 20% more freshman students a year.

Personal.—Dr. Theodore H. Ingalls, formerly associate professor of epidemiology, Harvard University School of Public Health, Boston, joined the University of Pennsylvania School of Medicine faculty July 1 as professor of preventive medicine and epidemiology and will direct a Kellogg Foundation research project aimed at evaluation of periodic health examinations for the early detection and prevention of chronic diseases. He will also be responsible for directing a graduate research and training program in the university's department of public health and preventive medicine, headed by Dr. John P. Hubbard.——Dr. Lincoln Godfrey Jr., of the University of Pennsylvania Medical School, has been appointed director for research of the National Council on Alcoholism Medical Research Committee. As director, Dr. Godfrey will make a survey of research in the basic sciences preparatory to developing specific programs in alcoholism research.——Dr. Donald M. Pillsbury, chairman, University of Pennsylvania School of Medicine's department of dermatology, has been named president of the 12th International Congress of Dermatology, to be held in Washington, D. C., in 1962.

WASHINGTON

Fishing Derby in Idaho.—Scenic Priest Lake in Northern Idaho will be the site of the Doctors' Fishing Derby to be held Sept. 15 as an event of the 1958 convention of the Washington State Medical Association, according to Dr. O. Charles Olson of Spokane, derby chairman. The fishing derby will be headquartered at Linger Lodge at Priest Lake. Round-trip bus transportation will be provided from the Davenport Hotel in Spokane, where the convention will be held Sept. 14-17. Boats and out-of-state licenses will be provided to participants in the derby, and breakfast, luncheon, and an evening banquet will be served.

Personal.—Dr. Charles A. Evans, professor of microbiology, University of Washington School of Medicine, Seattle, has been appointed a member of the National Advisory Cancer Council of the U. S. Public Health Service.——Dr. Robert F. Rushmer, professor of physiology and biophysics, University of Washington, Seattle, gave "Cinefluorographic Studies of Cardiac Function" as the third W. Edward Chamberlain Lectureship, presented by the department of radiology in cooperation with the department of physiology, Temple University School of Medicine, Philadelphia.——Dr. Henry S. Bennett, professor of anatomy, University of Washington School of Medicine, Seattle, has been appointed to the National Advisory Health Council to the U. S. Public Health Service.

WYOMING

State Medical Election.—The newly elected officers of The Wyoming State Medical Society are: president, Dr. Luther H. Wilmoth, Lander; president-elect, Dr. Benjamin Gitlitz, Thermopolis; vice-president, Dr. Francis A. Barrett Jr., Cheyenne; secretary, Dr. Silvio J. Giovale, Cheyenne; treasurer, Dr. Carleton D. Anton, Sheridan; delegate to A. M. A., Dr. Albert T. Sudman, Green River; alternate delegate to A. M. A., Dr. Bernard J. Sullivan, Laramie; and executive secretary, Mr. Arthur R. Abbey, Cheyenne.

GENERAL

Surgical Conference in Nassau.—The first Bahamas Surgical Conference will be held at the British Colonial Hotel in Nassau, Bahamas, Dec. 29-Jan. 17. Speakers will include the following:

Drs. Richard H. Barrett, Hanover, N. H.; Lowell F. Bushnell, Los Angeles; John M. Chamberlain, Carl T. Javert, Gerald H. Pratt, and Charles S. Rogers, New York City; Bertha N. Davis-Clark, Randolph L. Clark Jr., and William O. Russell, Houston, Texas; Lawrence S. Fallis and Walter H. Seegers, Ph.D., Detroit; Lewis K. Ferguson, Arthur Finkelstein, Robert P. Glover, Louis E. Silcox, and Henry J. Tumen, Philadelphia; James H. Ferguson, and Donald W. Smith, Miami; and Raymond H. Rigdon, Galveston, Texas.

Special rates are available by writing directly to the manager of the hotel. For information write Dr. B. L. Frank, 23 E. 79th St., New York 21.

Railway Surgeons Meet in Seattle.—The annual meeting of the Western Association of Railway Surgeons will be held Aug. 7-9 in Seattle and will open with the presidential address by Dr. Bernard E. McConville, of Seattle. The annual Dr. William T. Cummins Memorial Lecture, "The Surgery of Peptic Ulcer," will be presented by Dr. Edward B. Speir, Seattle. Other participants will include the following: Drs. William A. McMahon, Matthew H. Evoy, Carl E. Chism, James D. Layman Jr., William J. Kelly, John R. Mullins, Stephen J. Wood,

James F. Nelson, Carl J. Pinard Jr., J. Irving Tuell, and Dean K. Crystal, Seattle; William T. Duggan, San Francisco; and Roger W. Barnes, Los Angeles. A program of entertainment has been arranged, and the banquet will be held the evening of Aug. 8. For information write Dr. Graham J. Owens, Secretary, Western Association of Railway Surgeons, 906 Grand Ave., Kansas City 6, Mo.

Fellowships for Research and Clinical Medicine.—Deadlines for applications to the National Foundation for Infantile Paralysis, 301 E. 42nd St., New York 17, for postdoctoral fellowships in research and academic medicine or in the clinical fields of rehabilitation, orthopedics, and preventive medicine are Sept. 1 and Dec. 1. Financial support of the fellow varies according to his previous education, experience, marital status, and number of dependents. Compensation to the institution is arranged according to the program undertaken. For a full academic program, tuition and fees are allowed; for other programs, a sum not to exceed $1,250 per year (includes tuition) is provided. Awards are made on recommendation of the appropriate National Foundation Fellowship Committee. U. S. citizenship is required, but those who have filed a petition for naturalization will be considered. Partial fellowships are available for qualified veterans to supplement G. I. educational benefits.

Cardiac Conference in Denver.—The seventh annual Western Cardiac Conference, sponsored by the Colorado Heart Association, the Colorado State Department of Public Welfare, Fitzsimons Army Hospital, the University of Colorado School of Medicine, and the Veterans Administration Hospital, will be held Aug. 11-15 at the Phipps Auditorium, Denver. Guest speakers include Drs. Morgan Berthrong, Colorado Springs; Edwin Boyle Jr., Charleston, S. C.; William Dock, Brooklyn; Lt. Col. Laurence M. Hursch, M. C., U. S. Army, Denver; John W. Kirklin, Rochester, Minn.; Edward Massie, St. Louis; Henry J. L. Marriott, Baltimore; John H. Moyer, Philadelphia; and George E. Wakerlin, New York City. Conference topics include "Modern Concepts of Electrocardiographic Interpretation" (Aug. 11-12), "Seminar on Hypertension" (Aug. 13), and "Recent Advances in Cardiovascular Diseases" (Aug. 14-15). A clinical pathologic conference and exhibits are planned. At the annual dinner Aug. 14, Dr. Dock will present "The History of Coronary Artery Disease." For information write the Colorado Heart Association, 1636 Logan St., Denver 3.

Meeting of National Medical Association in Milwaukee.—The 63rd convention of the National Medical Association will be held Aug. 11-14 at the Hotel Schroeder, Milwaukee. Guest speakers will include Judge Scovel Richardson, Washington, D. C.; Dr. Raymond D. Puritt, Rochester, Minn.; and Dr. Holland T. Jackson, Fort Worth, Texas. Panel discussions at the section meetings will include the following topics and moderators:

The Acute Abdomen, Dr. James M. Whittico, Jr., St. Louis.
Treatment of the Common Dermatologic Conditions, Dr. Carter L. Marshall, New Haven, Conn.
Office Gynecology, Dr. Robert C. Stepto, Chicago.
New Horizons in Ophthalmology and Otolaryngology, Dr. Gerhard D. Straus, Milwaukee.
A Planned Approach to Doctor Distribution in Urban and Rural Areas, Dr. Hiram L. Bell, New York City.

The president's address will be given by Dr. Arthur M. Townsend Jr. A symposium on "Gastric Ulcer" will be presented at the surgical section with Dr. William H. Sinkler Jr., as moderator. The Charles R. Drew Memorial Forum of Fundamental Science, moderated by Dr. Ellsworth E. Hasbrouck, Chicago, will be held the morning of Aug. 14, with a clinical pathological conference, "Stump the Audience," to be held that afternoon. Scientific and technical exhibits and a ladies' program are planned. Entertainment includes the president's ball August 14. For information write the National Medical Association, Inc., 1108 Church St., Norfolk 10, Va.

Foreign Seminar Tour.—A medical exchange team of American physicians conducted a series of seminars on immunopathology with doctors in Paris, France; Cologne, Bonn, Heidelberg, Freiburg, and Berlin, Germany; Basle, Seelisburg, and Zurich, Switzerland; and Prague, Czechoslovakia, June 8-July 5, under the sponsorship of the Unitarian Service Committee, a nonsectarian voluntary social welfare agency with headquarters in Boston. Field expenses of the team are supported by a grant from the Miles-Ames Foundation of Indiana. Object of the mission is the exchange of research information, to aid the advance of knowledge in the science of immunopathology in all countries whose representatives participate in the several symposiums, including the United States. Chairman of the exchange team was Dr. Lewis Thomas, chairman, department of pathology, New York University College of Medicine, New York City. Other members were: Dr. Chandler A. Stetson Jr., New York City; Dr. Frank J. Dixon Jr., Pittsburgh; Dr. Baruj Benacerraf, New York City; Dr. Robert A. Good, Minneapolis; and Dr. Ernest Witebsky, Buffalo, N. Y. Dr. Witebsky received special honors at Heidelberg University, from whose faculty he was expelled by the Nazis before World War II. The Unitarian Service Committee was established in 1940 to help refugees escape from Nazi Europe, but over the years it has adapted its program to changing needs in the fields of social work, education,

medical exchange teams, community development, and rehabilitation carried on in Nigeria, Cambodia, Greece, Italy, France, and Germany.

San Francisco Golf Tournament Winners.—The recent annual tournament of the American Medical Golfing Association held on Olympic Club's two golf courses at Lakeside in San Francisco, was the largest attended in the 42-year history of the organization. The number of medical golfers who played was 374, and 350 of them stayed for the banquet in the evening, when more than $5,000 in prizes was distributed. There were 112 new members that participated in the tournament this year.

Dr. William O'Neal, of Pasadena, a surgeon, played even par 72 to win top honors. Dr. O'Neal has twice won the California State championship medal. Drs. Paul E. Travis, of Bell, Calif., and Frank Whittaker, of San Jose, Calif., both had gross scores of 73. The low net division was won by Dr. Gordon Erickson, of Encino, Calif. (62-12–64) and Dr. Fred Rice, of Indianapolis was second (94-28–66). Dr. Bob Reuter, of Fresno, Calif., made a hole in one on the fifth hole of the Ocean course.

Dr. Frank Whittaker, of San Jose, Calif., congratulates Dr. William O'Neal (holding trophy), of Pasadena, Calif. Dr. O'Neal stroked a par 72 to edge Dr. Paul Travis (second from left) and Dr. Whittaker (second from right) by one stroke. The low net division was topped by Dr. Gordon Erickson, of Encino, Calif. (far right), who finished two strokes ahead of Dr. Fred Rice, of Indianapolis (far left).

The winners of the eight flights were, in order: Drs. J. Dee Lansing, Arlington, Calif. (77-8–69); Winston Williams, El Segundo, Calif. (77-9–68), F. M. Binkley, San Francisco (79-12–67); J. H. Abramson, Sherman Oaks, Calif. (83-13–70); Ed Baker, Oakland, Calif. (84-15–69); John Growdon, Kansas City, Mo. (69); R. W. Burnett, Bakersfield, Calif. (68); and Robert Steeler, San Francisco (69).

The following officers were elected for the ensuing year: Dr. James McLaughlin, 1443 Cayugo St., Philadelphia, president; Dr. John Growdon, Kansas City, Mo., president-elect; Dr. Vincent deP. Larkin, Forest Hills, Long Island, N. Y., first vice-president; and Dr. William R. Smart, San Rafael, Calif., second vice-president.

The next tournament will be held at the Sea View Country Club, Atlantic City, N. J., June 8, 1959. Correspondence concerning membership should be addressed to Dr. McLaughlin at the above address.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	July 5, 1958 Paralytic Type	July 5, 1958 Total Cases	July 6, 1957 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	..	1	1
Rhode Island	..	..	..
Connecticut	1	1	..
Middle Atlantic States			
New York	2	3	4
New Jersey	..	1	..
Pennsylvania	..	1	..
East North Central States			
Ohio	..	..	2
Indiana	..	1	2
Illinois	..	..	3
Michigan	..	1	6
Wisconsin	2	2	4
West North Central States			
Minnesota	..	..	..
Iowa	..	..	2
Missouri	..	1	3
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	1	2
Kansas	..	..	1
South Atlantic States			
Delaware	..	..	1
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	2	2	2
West Virginia	2	2	..
North Carolina	..	1	6
South Carolina	..	..	5
Georgia	1	1	3
Florida	1	8	..
East South Central States			
Kentucky	1	1	..
Tennessee	1	2	11
Alabama	1	1	1
Mississippi	..	5	2
West South Central States			
Arkansas	1	1	3
Louisiana	3	4	12
Oklahoma	..	3	5
Texas	8	12	45
Mountain States			
Montana	1	3	..
Idaho	..	..	1
Wyoming	..	..	..
Colorado	..	..	1
New Mexico	1	1	1
Arizona	..	..	..
Utah	..	..	2
Nevada	..	..	1
Pacific States			
Washington	..	..	..
Oregon	1	1	1
California	1	2	13
Territories and Possessions			
Alaska	..	..	..
Hawaii	4	4	..
Puerto Rico	..	..	1
Total	34	67	147

FOREIGN

International Congress of Balneology.—The Czechoslovak Society of Physiotherapy is holding an International Congress of Balneology in Marienbad Sept. 8-13. One day will be devoted to choledocholithiasis, with an excursion to Karlovy Vary, Carlsbad. Papers will be read by scientists from Bulgaria, France, the German Democratic Republic, the German Federal Republic, Hungary, Poland, the Soviet Union, Sweden, and Czechoslovakia. The official languages of the Congress are English, French, Russian, German, Czech, and Slovak, and there will be simultaneous interpretation. Excursions and social events and a special program for family members of participants are planned. Inquiries should be addressed to the Secretary of the International Congress of Balneology, Reznická 5, Prague 2, Czechoslovakia.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral Examination.* San Francisco, Sept. 29-Oct. 3, and Phoenix, April 5-10, 1959. The 1959 written examination will be given in various locations in the United States and Canada, July 17. The final date for filing application for the 1959 written examination is six months prior to the examination. There is no filing deadline for oral examinations. Sec., Dr. Curtiss B. Hickcox, 217 Farmington Ave., Hartford 8, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Written. Several Cities,* June 30. *Oral.* Detroit, Oct. 17-19. Final date for filing all applications is April 1. Sec., Dr. Beatrice Maher Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 20, 1958. *Oral.* Chicago, Oct. 13-16. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Applications for certification, new and reopened, Part I, and requests for re-examination Part II, are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of application is September 1, 1958. No application can be accepted after that date. It should be noted by prospective candidates that the deadline date in 1959 is August 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written,* qualifying test (Part 1), January 1959. Final date for filing application was July 1, 1958. *Oral Examinations 1958* (Part II): Chicago, Oct. 17-22. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* Chicago, Jan. 21-23, 1959. Deadline for receipt of applications is Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Avenue, Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral.* Chicago, Oct. 6-10. Final date for filing application was April 30. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: Chicago, Oct. 30-Nov. 1. Final date for filing application is Sept. 30. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Chicago, Oct. 24-26 and New York, Dec. 5-7. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* Chicago, Oct. 9-11. Final date for receipt of case reports was July 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Examination in Public Health.* St. Louis, Oct. 24-26. Final date for filing application is Aug. 15. Sec., Dr. Thomas F. Whayne, 3438 Walnut St., Philadelphia 4.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written, Parts I and II.* September 1958. Final date for filing application is March 15. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York City, Dec. 15-16; New Orleans, Mar. 16-17. Training credit for full time psychiatric and/or neurologic assignment in unapproved military programs or services between the dates of Jan. 1, 1950 and Jan. 1, 1954 will be terminated on Jan. 1, 1959. Sec., Dr. David A. Boyd, 102-110 Second Ave. S. W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Regular Examination.* Washington, D. C., Dec. 8. Final date for filing application was July 1. *Special examination in Nuclear Medicine for those diplomates in Radiology or Therapeutic Radiology.* Washington, D. C., Dec. 6. Final date for filing application is Oct. 1. *Special Examination.* Cincinnati, Mar. 16-19, 1959. Final date for filing application is Nov. 1. Candidates completing training June 30, 1959 are not eligible for the Spring 1959 examinations. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: Written examinations (Part 1) will be held at various centers in the United States, Canada, Hawaii, Puerto Rico, and certain military centers abroad on December 3. The date of the Fall examination in *Part I* has been changed from the last Wednesday of October as announced in its current Booklet of Information to December 3, 1958. Thereafter, examinations in Part I will be held once annually, on the first Wednesday of December. The closing date for filing applications will be August 1. *Part II.* Philadelphia, Sept. 15-16; Rochester, Minn., Oct. 20-21; Nashville, Tenn., Nov. 17-18; New York City, Dec. 15-16; Houston, Tex., Jan. 12-13; New Haven, Conn., Feb. 9-10; Durham, No. Car., March 9-10; San Francisco, April 13-14; Indianapolis, May 11-12; Columbus, Ohio, May 14-15. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

BOARD OF THORACIC SURGERY: Various centers throughout the United States. *Written.* Sept. 12. Final date for filing application was July 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Avenue, Detroit 2.

AMERICAN BOARD OF UROLOGY: *Written Examination.* Twenty-five cities throughout the country, Dec. 5. The oral will be given in Chicago in February 1959. Sec., Dr. William Niles, Wishard, Jr., 30 Westwood Road, Minneapolis 26.

DEATHS

Adkins, Onan Charles ✱ Indianapolis; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1907; served in France during World War I; died May 26, aged 81, of myocarditis.

Bassett, Alice Haley ✱ Boston; Boston University School of Medicine, 1898; died April 10, aged 89, of pernicious anemia.

Betz, Jonathan Clymont, Baltimore; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1899; died in the Johns Hopkins Hospital May 20, aged 79, of chronic asthmatic bronchitis.

Bitter, Harry, Brooklyn; University of Arkansas School of Medicine, Little Rock, 1927; member of the Medical Society of the State of New York and the American Academy of General Practice; died in the Williamsburg General Hospital March 24, aged 57, of coronary thrombosis.

Breco, Joseph Gideon, Corpus Christi, Texas; Southwestern University Medical College, Dallas, 1905; an associate member of the American Medical Association; member of the Oklahoma State Medical Association; practiced in Ada, Okla.; died in the Spohn Hospital May 23, aged 80, of ruptured abdominal aortic aneurysm.

Butler, Harry Herbert, Brookline, Mass.; Boston University School of Medicine, 1919; formerly associated with the Veterans Administration; died in the Veterans Administration Hospital, West Roxbury, Boston, May 5, aged 76, of cancer.

Calcagni, Oscar Henry ✱ Morrisville, Vt.; University of Vermont College of Medicine, Burlington, 1936; veteran of World War II; on the staff of the Copley Hospital; died in Burlington May 2, aged 49.

Caldwell, Joseph Ridgely, Short Creek, W. Va.; Rush Medical College, Chicago, 1896; an associate member of the American Medical Association; past-president and vice-president of the Ohio County Medical Society; fellow of the American College of Surgeons; formerly practiced in Wheeling, where he was a member of the city council; served on the staffs of the Ohio Valley General and Wheeling hospitals in Wheeling; died June 7, aged 85.

Carnett, William Wallace, Formosa, Ark. (licensed in Arkansas in 1903); died in Little Rock May 22, aged 89.

✱ Indicates Member of the American Medical Association.

Caswell, Harlow Orton ✱ Jefferson, Wis.; Rush Medical College, Chicago, 1897; headed the county draft board during World Wars I and II and received a citation from President Roosevelt for his work; surgeon for the Northwestern Railroad; on the honorary staff, Fort Atkinson (Wis.) Memorial Hospital; assistant resident physician at the Jefferson County Hospital; died May 12, aged 84, of coronary thrombosis.

Civins, Albert Isaac, Cleveland; University of Wooster Medical Department, Cleveland, 1901; died May 16, aged 81, of cancer of the colon and liver.

Collier, Casa ✱ Memphis, Tenn.; Northwestern University Medical School, Chicago, 1910; fellow of the American College of Surgeons; veteran of World War I; died May 11, aged 72.

Conkey, Ogden Fethers, Canton, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1912; at one time on the faculty of Cornell University Medical College in New York City; died June 2, aged 72, of cerebral hemorrhage.

Conner, Elwin Kerr ✱ Filer, Idaho; University of Nebraska College of Medicine, Omaha, 1954; certified by the National Board of Medical Examiners; died in the Bishop Clarkson Memorial Hospital, Omaha, May 3, aged 30, of cancer of the pancreas.

Cooley, Samuel Studdiford ✱ Black Mountain, N. C.; University and Bellevue Hospital Medical College, New York City, 1934; specialist certified by the American Board of Internal Medicine; member of the American Trudeau Society; veteran of World War II; served on the staffs of the Memorial Mission Hospital of Western North Carolina in Asheville, Fellowship Sanatorium of the Royal League, and the Western North Carolina Sanatorium; died in Asheville May 9, aged 52, of coronary thrombosis.

Cornell, John Cecil ✱ St. Louis; St. Louis University School of Medicine, 1909; served overseas during World War I; on the staff of St. Anthony's Hospital; died May 17, aged 71, of cancer.

Corrigan, Patrick Henry ✱ Trenton, N. J.; born in Newark, Dec. 18, 1900; Georgetown University School of Medicine, Washington, D. C., 1923; past-president of the Mercer County Medical Society; secretary of the New Jersey Board of Medical Examiners; member of the Association for Research in Nervous and Mental Disease; specialist certified

by the American Board of Internal Medicine; a trustee of the Medical-Surgical Plan of New Jersey; consultant, F. W. Donnelly Memorial Hospital and the Orthopaedic Hospital and Dispensary; on the staff of St. Francis Hospital, where he died May 28, aged 57, of myocardial infarction, and hypertensive cardiovascular disease.

Cowan, Clyde Robert ✱ Buzzards Bay, Mass.; Middlesex College of Medicine and Surgery, Cambridge, 1915; College of Physicians and Surgeons, Boston, 1917; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; for many years practiced in Boston; died May 10, aged 74.

Cremin, Lawrence Dennis, Riviera Beach, Fla.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1914; veteran of World War I; died in the Veterans Administration Hospital in Coral Gables, April 1, aged 71, of carcinoma of the colon with metastases.

Damiani, Pasquale George ✱ Peru, Ind.; Hahnemann Medical College and Hospital of Philadelphia, 1925; formerly practiced in Philadelphia, where he was on the faculty of his alma mater, and on the staffs of the Hahnemann and Women's Homeopathic hospitals; chief of staff, Dukes–Miami County Hospital; died May 19, aged 58, of coronary thrombosis.

Davidson, Edward Young ✱ Washington, D. C.; Columbian University Medical Department, Washington, 1894; in 1916 president of the Medical Society of the District of Columbia and was instrumental in the planning and erection of its present building, where his portrait now hangs; in 1941 was awarded the society's Order of Merit for the most worthwhile contribution to the society and in 1929 it recognized his services by establishing the Davidson Lecture; died in the Eastern Star Masonic Home May 22, aged 97, of carcinoma of the colon.

Dawley, Walter Averill ✱ Rapid City, S. D.; University of Illinois College of Medicine, Chicago, 1926; fellow of the American College of Surgeons; immediate past-president of the South Dakota Cancer Society; served as a member of the school board; associated with the Homestead Hospital in Lead and Bennett Memorial and St. John's McNamara hospitals; died May 30, aged 58, of cerebral hemorrhage.

De Bell, Arthur Wise, Malden, W. Va.; University of the South Medical Department, Sewanee, Tenn., 1903; veteran of World War I; died May 22, aged 84.

Denton, Aulsey Leo, Castalia, N. C.; Medical College of Virginia, Richmond, 1918; veteran of World War I; died April 9, aged 68, of pulmonary emphysema, chronic bronchitis, and esophageal stenosis.

Denyes, Orville Leston ✱ Momence, Ill.; Chicago Medical School, 1931; veteran of World War II; on the staff of St. Mary's Hospital in Kankakee; surgeon for the Chicago and Eastern Illinois Railroad; died May 30, aged 57, in an automobile accident.

De Weese, Charles W., Livermore, Ky.; Hospital College of Medicine, Louisville, 1906; veteran of the Spanish–American War; died May 16, aged 77, of a heart attack.

Dickinson, Marion Franklin, Little Rock, Ark.; University of Arkansas School of Medicine, Little Rock, 1919; died May 18, aged 79, of cancer.

Dohm, Arthur J., St. Paul; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1906; served as police surgeon; died in the Miller Hospital May 14, aged 77, of ventricular fibrillation and coronary sclerosis.

Donnelly, Leo Charles, Detroit; Detroit College of Medicine, 1911; died in Dansville, Mich., May 30, aged 68.

Dupras, Joseph Elzear, Auburn, Maine; Laval University Faculty of Medicine, Quebec, Que., Canada, 1906; member of the staff of the Central Maine General Hospital; died May 15, aged 77.

Eifert, Elmer Ernest ✱ Alfordsville, Ind.; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1907; veteran of World War I; on the staff of the Daviess County Hospital in Washington, where he died May 13, aged 73, of pernicious anemia.

Elarbee, George Wiley ✱ Pahokee, Fla.; Atlanta College of Physicians and Surgeons, 1900; on the staff of the Everglades Memorial Hospital; died in West Palm Beach May 26, aged 82, of intestinal obstruction.

Emy, Saburo ✱ New York City; University and Bellevue Hospital Medical College, New York City, 1922; member of the American Society of Anesthesiologists; veteran of World War I; director of anesthesiology at the Misericordia Hospital, where he died May 20, aged 68, of cancer.

Etheridge, Carl Eugene ✱ Tuscaloosa, Ala.; University of Arkansas School of Medicine, Little Rock, 1929; on the staff of the Bryce Hospital; died in the Methodist Hospital, Rochester, Minn., May 21, aged 57, of cancer of the esophagus.

Fasting, George Frederick Christopher ✱ New Orleans; Rush Medical College, Chicago, 1926; served on the faculty of Louisiana State University School of Medicine; senior bacteriologist at Charity Hospital; died May 26, aged 66, of acute myocardial infarction.

Field, Martin Thomas ✻ Salem, Mass.; Harvard Medical School, Boston, 1901; fellow of the American College of Surgeons; served as city physician and member of the health board; consultant at Salem Hospital; died May 22, aged 82.

Fine, Abraham, Woodmere, L. I., N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1906; veteran of World War I; formerly associated with the Mount Sinai Hospital in New York City; died June 4, aged 76.

Foust, Earl William ✻ Royal Oak, Mich.; Detroit College of Medicine and Surgery, 1928; veteran of World War II; served on the staff of the Mount Carmel Mercy Hospital, Detroit, where he died May 19, aged 59.

Gale, Joseph, Miami Beach, Fla.; University of Illinois College of Medicine, Chicago, 1923; died May 14, aged 60, of cirrhosis of the liver.

Gantz, Frank Elwin ✻ Washington, D. C.; George Washington University School of Medicine, Washington, 1926; member of the Industrial Medical Association; veteran of World War I; died in the Doctors Hospital May 23, aged 61, of cancer of the prostate.

Geis, Neil Charles ✻ Chicago; Chicago College of Medicine and Surgery, 1913; member of the staff of Ravenswood Hospital; died June 3, aged 70.

Geraci, Frank Paul ✻ Cleveland; Western Reserve University School of Medicine, Cleveland, 1917; fellow of the American College of Surgeons; veteran of World War I; on the staff of the Grace, St. Alexis, and Huron Road hospitals; died May 7, aged 66, of coronary thrombosis.

Gilmore, Rowland Thomas S. ✻ Bemidji, Minn.; Trinity Medical College, Toronto, Ontario, Canada, 1895; fellow of the American College of Surgeons; died in Durand April 14, aged 88.

Giuliana, Robert Amedeo ✻ Newark, N. J.; Long Island College Hospital, Brooklyn, 1898; served as president of the Physicians' Art Association of New Jersey; associated with the St. James Hospital, of which he was one of the founders; on the staffs of the Monmouth Memorial and Hazard hospitals in Long Branch and St. Vincent's Hospital in Montclair; died in Monmouth Beach May 28, aged 80, of coronary occlusion.

Gliedman, Lester Howard ✻ Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1950; assistant professor of psychiatry at his alma mater; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; veteran of World War II; associated with the Johns Hopkins Hospital; died May 20, aged 39, in a plane crash.

Gordon, John Kyle, Chambersburg, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1904; an associate member of the American Medical Association; for many years member and president of the school board; on the staff of the Chambersburg Hospital; died May 20, aged 80, of carcinoma of the colon.

Grandfield, Robert Francis, Millis, Mass.; Middlesex University School of Medicine, Cambridge, 1927; died in the Framingham Union Hospital in Framingham May 17, aged 61, of cerebral thrombosis.

Gray, William Harry, Broadwater, Neb.; Lincoln Medical College of Cotner University, 1904; died May 7, aged 82, of diabetes mellitus.

Griffith, Mose Simpson ✻ Galesburg, Ill.; Miami Medical College, Cincinnati, 1907; veteran of World War I; associated with Cottage Hospital and St. Mary's Hospital, where he died May 4, aged 74.

Guinan, Edward Robert, Los Altos, Calif.; Cooper Medical College, San Francisco, 1911; an associate member of the American Medical Association; fellow of the American College of Surgeons; member of the American Academy of General Practice; served during World War I; later served in the regular Navy; for many years chief of staff of Richmond (Calif.) Hospital; died in the Palo Alto (Calif.) Hospital May 26, aged 69, of congestive heart disease and pneumonia.

Hanes, Charles Benjamin ✻ Ambler, Pa.; Jefferson Medical College of Philadelphia, 1947; interned at the Chestnut Hill Hospital in Philadelphia, where he served a residency and where he died May 30, aged 35, of injuries received in an automobile accident.

Hannum, Edwin Alan, Birmingham, Mich.; University of Wooster Medical Department, Cleveland, 1904; formerly practiced in Cleveland, where he was on the staff of the Lakeside Hospital; died in St. Joseph's Mercy Hospital, Pontiac, May 22, aged 85.

Harnett, David Louis ✻ Chicago Heights, Ill.; Northwestern University Medical School, Chicago, 1926; member of the Aero Medical Association and the Industrial Medical Association; veteran of World War I; on the staff of the St. James Hospital; died in the Edgewater Hospital, Chicago, May 27, aged 63, of perforated gastric ulcer.

Herbert, Howard Beaman, Chicago; Chicago Medical School, 1933; member of the American Academy of General Practice; died in the Michael Reese Hospital June 8, aged 60, of myocardial infarction and coronary arteriosclerosis.

Herkimer, Daniel Robert ✻ Lincoln Park, Mich.; Detroit College of Medicine and Surgery, 1927; member of the American Fracture Association; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World Wars I and II; served on the staffs of the William Booth Memorial and Mount Carmel Mercy hospitals in Detroit, Wyandotte (Mich.) General Hospital, Oakwood Hospital, Dearborn, and Outer Drive Hospital; for many years health officer; died May 11, aged 62, of acute right ventricular failure.

Herweg, Janet Ruth Scovill, Brentwood, Mo.; Columbia University College of Physicians and Surgeons, New York City, 1943; certified by the National Board of Medical Examiners; interned at Barnes Hospital, St. Louis, where she served a residency; served a residency at St. Louis Children's Hospital in St. Louis; died in the Barnes Hospital, St. Louis, May 11, aged 39, of cancer.

Hudack, Stephen Sylvester ✻ Enumclaw, Wash.; born in Cleveland Aug. 1, 1900; Western Reserve University School of Medicine, Cleveland, 1929; served as assistant clinical professor of surgery at his alma mater; at one time instructor in surgery and associate professor of orthopedic surgery at Columbia University College of Physicians and Surgeons in New York City, where he served in many capacities at the Presbyterian Hospital; director and founder of research in the division of surgery at St. Luke's Hospital in Cleveland; since September, 1957, surgical consultant at the Community Memorial Hospital; veteran of World War II; fellow of the New York Academy of Medicine and the American College of Surgeons; member of the Harvey Society, American Society for Experimental Pathology; American Association for the Surgery of Trauma, American Association for the Advancement of Science; died May 13, aged 57, of coronary occlusion.

King, Edward Philip ✻ Chicago; Loyola University School of Medicine, Chicago, 1926; veteran of World War II; on the staff of St. Anne's Hospital; died June 6, aged 58, of acute myocardial infarction.

Kirschbaum, Arthur, Houston, Texas; born in New York City Oct. 15, 1910; University of Minnesota Medical School, Minneapolis, 1943; professor and chairman of the department of anatomy at Baylor University College of Medicine and the University of Texas Dental Branch; teaching assistant in zoology at his alma mater from 1931 to 1934, teaching fellow of anatomy from 1934 to 1937, instructor, 1941-1942, assistant professor from 1942 to 1945, and associate professor of anatomy from 1945 to 1951; instructor of anatomy at Yale in New Haven, Conn., 1938-1939 and 1940-1941; professor and head of the department of anatomy at the University of Illinois College of Medicine in Chicago from 1951 to 1954; member of the American Association for Cancer Research and secretary of the Southwest Section; member of the American Society for Experimental Pathology, International Association for Dental Research, Sigma Xi, Phi Beta Kappa, and the American Association for the Advancement of Science; in 1951 recipient of the Minnesota State Award of the American Cancer Society; recently appointed professional member of the National Advisory Health Council of the National Institutes of Health; consultant for the U. S. Public Health Service; consulting experimental hematologist for the University of Texas, M. D. Anderson Hospital and Tumor Institute; consultant, Veterans Administration Hospital; served as an advisory editor of *Cancer Research;* died in the Methodist Hospital May 28, aged 47, of myocardial infarction.

Knutson, Anton ✻ Reynolds, Ill.; Chicago College of Medicine and Surgery, 1941; served on the staff of the Lutheran Hospital in Moline; accidentally drowned while fishing in Parent Lake, in Northern Minnesota, May 25, aged 73.

Laszlo, Daniel, New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1926; member of the Medical Society of the State of New York; specialist certified by the American Board of Internal Medicine; fellow of the American Association for the Advancement of Science; member of the American Association for Cancer Research; chief of the division of neoplastic diseases at Montefiore Hospital; died June 1, aged 55.

Learoyd, Charles Berry ✻ Danvers, Mass.; College of Physicians and Surgeons, medical department of Columbia College, New York City, 1887; died in Waltham May 13, aged 98, of bronchopneumonia.

MacKinlay, Edgar Harold ✻ McConnellsburg, Pa. Columbia University College of Physicians and Surgeons, New York City, 1929; certified by the National Board of Medical Examiners; director of public health of Fulton County; for many years county coroner; president of the First National Bank; on the staffs of the Fulton County Medical Center in McConnellsburg and Chambersburg (Pa.) Hospital, where he died May 10, aged 53, of cancer.

Martin, William S. ✻ Memphis, Tenn.; Meharry Medical College, Nashville, Tenn., 1907; owner of the Memphis Red Sox Baseball Club and Martin Stadium; president of the medical staff and for many years superintendent of the Collins Chapel Correctional Hospital, where he died May 17, aged 78.

Masucci, Alberico ✻ Paterson, N. J.; Boston University School of Medicine, 1930; fellow of the American College of Surgeons; on the staff of St. Joseph's Hospital; died April 18, aged 50, of asthma and an anaphylactic reaction following a third injection of "anti-polio vaccine."

Melzer, Fred John, Cleveland; University of Wooster Medical Department, Cleveland, 1908; served on the staff of the Polyclinic Hospital; died in the Mound Park Hospital, St. Petersburg, May 8, aged 71, of bronchogenic cancer.

Otis, Frank Jesse ✻ Moline, Ill.; born in San Jose, Calif., April 22, 1873; American Medical Missionary College, Battle Creek, Mich., and Chicago, 1899; Rush Medical College, Chicago, 1908; served on the faculty of the American Medical Missionary College in Battle Creek, Mich., and Chicago; fellow of the American College of Surgeons; formerly on the staff of the Battle Creek (Mich.) Sanitarium; at one time physician in charge of the Tri-City Sanitarium; associated with the Lutheran and Moline Public hospitals in Moline and the St. Anthony's Hospital in Rock Island; died in Loma Linda, Calif., May 8, aged 85, of acute coronary occlusion.

Parker, Carl Horace, Carmel Valley, Calif.; Rush Medical College, Chicago, 1909; specialist certified by the American Board of Radiology; an associate member of the American Medical Association; member of the American Roentgen Ray Society; formerly practiced in Pasadena, where he was on the staff of the Collis P. and Howard Huntington Memorial Hospital; died in Pasadena May 8, aged 75, of acute myocardial infarction.

Patton, Mathew Morrison ✻ Spokane, Wash.; Northwestern University Medical School, Chicago, 1907; specialist certified by the American Board of Pathology; member of the College of American Pathologists; past-president of the Pacific Northwest Society of Pathologists; on the staff of the Sacred Heart Hospital; died in the Deaconess Hospital May 10, aged 78, of arteriosclerosis.

Pentecost, James Biggars, Winters, Texas; Southwestern University Medical College, Dallas, 1906; served as city health officer; died in the Hendrick Memorial Hospital, Abilene, May 11, aged 87, of angina pectoris.

Phillips, Clovis Hamilton ✻ Cleveland; University of Cincinnati College of Medicine, 1929; specialist certified by the American Board of Obstetrics and Gynecology; veteran of World War II; served on the faculty of Western Reserve University School of Medicine; associated with Lakeside and Veterans Administration hospitals; died in Rye Beach, N. H., May 29, aged 55, of cancer of the esophagus.

Presser, Karl ✻ New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1924; served on the staffs of the Beth Israel Hospital in Boston and the Montefiore Hospital; died in the Mount Sinai Hospital May 25, aged 59, of cancer.

Ryan, James Bernard ✻ Easthampton, Mass.; Tufts College Medical School, Boston, 1920; veteran of World War I; served for three terms as medical examiner for the Second Hampshire District from Massachusetts; school physician in Easthampton and Southampton; medical adviser of the medical care plan of the Easthampton Welfare Department; on the courtesy staffs of the Cooley Dickinson Hospital in Northampton and the Providence Hospital in Holyoke; died May 13, aged 61, of coronary thrombosis.

Sabatini, Felix Raphael, New York City; Fordham University School of Medicine, New York City, 1921; member of the Medical Society of the State of New York; died May 4, aged 61, of coronary thrombosis.

Schwing, Harold Edward ✻ Sacramento, Calif.; University of Buffalo School of Medicine, 1923; member of the American Academy of General Practice and the Industrial Medical Association; member of the Mercy Hospital staff; died May 18, aged 63.

Shick, Mary McDowell, Elwyn, Pa.; Woman's Medical College of Pennsylvania, Philadelphia, 1895; an associate member of the American Medical Association; for many years associated with the Elwyn Training School, where she died May 23, aged 92, of cancer.

Slabey, John Martin ✻ New York City; Denver College of Medicine, 1898; served on the staffs of the St. John's, Gotham, and Medical Arts Center hospitals; died May 25, aged 81, of pulmonary infarction.

Tchertkoff, Iekoussiel G., New York City; Universite de Paris Faculte de Medecine, France, 1913; associated with Sea View Hospital in Staten Island and the Metropolitan Hospital; died June 1, aged 73, of myocardial infarction.

Wallace, Louis Osgood Sanborn ✻ Manchester, N. H.; Maryland Medical College, Baltimore, 1912; member of the Association for Research in Nervous and Mental Disease; fellow of the American College of Physicians; veteran of World War I; suffocated May 20, aged 70, when his home was destroyed by fire.

Walter, Earle Charles, Mayfield, Ky.; Vanderbilt University School of Medicine, Nashville, Tenn., 1919; for many years associated with the Mayfield Hospital, where he died May 13, aged 63, of intestinal obstruction.

Ward, Michael Walter, Bangor, Wis.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1904; served as president of the La Crosse County Medical Society, president of the village, president of the school board, and director of the Bangor Telephone Company; on the staff of St. Mary's Hospital in Sparta; died May 13, aged 80, of heart disease.

FOREIGN LETTERS

INDIA

Benactyzine in Psychoneurosis.—N. S. Vahia and co-workers (*Indian Journal of Medical Sciences*, vol. 12, February, 1958) treated 28 psychoneurotic patients with benactyzine, an anticholinergic drug with mild atropine-like action. All were treated as outpatients. Most were diagnosed as having an anxiety state or a psychogenic headache. They were given one 1-mg. tablet three times a week for the first two weeks followed by two tablets three times a day for a further period of one week. An immediate subjective improvement was observed. More than 25% improvement was seen in eight patients on a dosage of 1 mg. three times a day and in six patients on a dosage of 2 mg. a day. Benactyzine therapy was stopped in one patient because of worsening of symptoms. An increase of dosage from 3 to 6 mg. per day did not produce any significant improvement in the results. With 3 mg. a day, no toxic manifestations were noted; but on the increased dosage, patients complained of giddiness, which was so marked in one case that the use of the drug had to be discontinued.

Hyaluronidase for Dermatoses.—B. B. Gokhale (*Indian Journal of Dermatology and Venereology*, vol. 24, Jan.-March, 1958) observed that the cellular infiltration and reactionary growth of connective tissue that occurs in the chronic lesions of some dermatoses is in a large measure responsible for their chronicity. To overcome this factor, the author tried local injections of hyaluronidase in conjunction with certain other drugs in a series of 11 patients (2 with lichen planus hypertrophicus or verrucosus, 1 with sycosis muchae, 2 with lupus vulgaris verrucosus of the hands and feet, 2 with lichen simplex, one with pigmented circumscribed patches, and 3 with tuberculoid leprotic macules). They were given local injections of 150 units of hyaluronidase dissolved in 1 or 2 cc. of isotonic saline solution. These injections were painful even when a 2% procaine solution was used as the solvent. The injections were given once a week or once in two weeks, the usual course of treatment being 8 to 12 injections depending on the nature and size of the lesion. In addition to the hyaluronidase, 500,000 units of penicillin, 0.5 Gm. of streptomycin, 0.5 cc. of ethyl ester of hydnocarpus oil for the first injection and then increasing by 0.25 cc. for every following injection, or calcium-PAS in doses of 0.5 to 1 cc. of a 10% solution was injected. Eight of the patients showed a satisfactory result. One patient with lupus vulgaris developed an abscess which was incised and the final result was satisfactory. Two developed bullae on the treated areas, one being a patient with a tuberculoid leprotic macule and the other a patient with a chronic pigmented patch of 10 years' duration. On the whole the results were satisfactory clinically and cosmetically.

Hypoglycemic Action of Toluylene.—P. S. Haranath and co-workers (*Indian Journal of Medical Sciences*, vol. 12, February, 1958) studied the blood sugar–reducing properties of pure substances derived from some indigenous drugs and their synthetic analogues. One of these, Pterocarpus marsupium, is reputed to possess antidiabetic properties. One of the authors extracted pterotoluylene in a pure state from the heartwood of Pterocarpus marsupium, which was found to have a hypoglycemic action. A synthetic analogue of this drug was also prepared, and the actions of these two compounds was studied on the fasting blood sugar in dogs. Both the compounds being sparingly soluble in water, alcoholic solutions were prepared for intravenous injection and the blood sugar level determined before and at frequent intervals after the injection of the drug. Pterotoluylene produced a fall in blood sugar of 26 to 50% on intravenous administration in a dosage of 10 mg. per kilogram of body weight. Larger doses (20, 30, and 50 mg. per kilogram of body weight) reduced the blood sugar after an initial period of hyperglycemia. This fall lasted longer than the five-hour observation period. The synthetic analogue was also found to possess a hypoglycemic action on intravenous administration in doses of 0.5 to 2.0 mg. per kilogram of body weight. Larger doses (4 or 5 mg. per kilogram of body weight) reduced the blood sugar level after an initial rise.

Thus both the compounds showed a hypoglycemic action in smaller dosage, while with a larger dosage there was an initial period of hyperglycemia. The mode of this action is not clear. The action was more marked with pterotoluylene than with the synthetic compound. The blood pressure was reduced by pterotoluylene given intravenously to anesthetized dogs. This action was not abolished by vagotomy, atropinization, or administration of antihistamines. With larger doses, apnea and increased rate of respiration were seen. The splenic volume was reduced. Pterotoluylene in larger doses

The items in these letters are contributed by regular correspondents in the various foreign countries.

proved toxic to two dogs who died at the end of 12 and 36 hours respectively after an initial period of listlessness and profuse salivation followed by dyspnea. With smaller doses no toxic effects were noticed in dogs at the end of the 10-day observation period.

Smallpox and Cholera.—The Union Health Ministry recommended to state governments investigation of the causes of the recent rise in the incidence of smallpox and cholera. The government of India has also requested the Indian Council of Medical Research to set up an expert committee for a similar purpose. The Health Ministry recommended that (1) the state governments consider whether the present system of registration of births in rural areas is satisfactory, as nonregistration of all live births results in the escape of many infants from primary smallpox vaccination; (2) revaccination be made compulsory; and (3) the reliability of the smallpox vaccine being used be investigated. Irregularity of the supplies also interfered with the satisfactory working of the vaccination program. Regarding cholera, the ministry recommended stockpiling of the necessary anticholera drugs, disinfectants, and water sterilizing agents; regular disinfection of all sources of water supply three weeks prior to the usual cholera season and thereafter at regular intervals; strict control over sanitation in fairs and festivals and compulsory inoculation of all persons attending these; and enforcement by all municipalities of sanitary regulations during this period.

Blood Histamine in Peptic Ulcer.—Basu Malik and Bhattacharya (*J. Indian M. A.* **30**:9 [May 1] 1958) studied a series of 20 patients with chronic peptic ulcers to determine whether there is any correlation between the basal acid secretion and the blood histamine level. The diagnosis in these patients was confirmed by roentgenography, and the blood was collected when the disease was in the active stage. The level in all these patients except one was found to be within the normal range, varying from 1 to 8 mcg. per 100 ml. In only one was the value high (17.5 mcg. per 100 ml.). No correlation could be found between the blood histamine level and the basal acid secretion of gastric juice.

Tolbutamide.—N. J. Mody (*J. A. Physicians India* **6**:2 [April] 1958) stated that tolbutamide had a marked hypoglycemic action in both diabetic and normal persons. In the treatment of properly selected diabetics it has a definite place. The best method of assessing the orally given hypoglycemic drugs is to study three-hourly blood sugar patterns with and without the drug, as these give a better idea about the action of the drug than studying only the glucose tolerance. Of his 22 patients 6 were receiving carbutamide prior to the trial. One of these developed intolerance to carbutamide and was therefore changed over to tolbutamide therapy, and one, though fully controlled by carbutamide, failed to respond to tolbutamide. Eighteen patients were between 40 and 60 years of age, two were below 40 (25 and 30), and two were over 60. One patient put on 6 lb. after treatment with tolbutamide and another lost 6 lb. Both were well controlled by the drug.

Each patient's diet was studied and adjusted after admission according to the desired weight for his height. Fourteen had taken 20 to 80 units of insulin daily. Nine had a family history of diabetes. Tolbutamide was started after about five days of hospitalization and dietary adjustment; 4 Gm. were given in four equal doses on the first day followed by 3, 2.5, and 2 Gm. on successive days. Six patients were fully controlled by this regimen. Their average fasting blood sugar level was 227 mg. per 100 cc., and the average after therapy with the drug was 105 mg. per 100 cc. One of these patients was an obese woman aged 65 years with a diabetes of 15 years' duration. Her condition was previously controlled with carbutamide, but tolbutamide was substituted because she developed an itching rash. The rash disappeared, and the disease was kept under control with tolbutamide. No side-effects were noticed in any of the patients. Seven who had a more advanced diabetes than the six mentioned above, with an average fasting blood sugar of 242 mg. per 100 cc., had a fair result, the average fasting blood sugar level after treatment coming down to 152 mg. per 100 cc. Nine patients were not benefited. Two of these had juvenile diabetes.

Another patient, also a juvenile, responded fairly well to tolbutamide. The average fasting blood sugar in this last group was 207.6 mg. per 100 cc. before treatment and 137.5 mg. per 100 cc. after treatment. No side-effects were noticed in any of these patients except one who complained of giddiness. There was no evidence of euphoria, and one patient complained of a sense of depression. The renal threshold was not affected by the drug. As compared to therapy with carbutamide, that with tolbutamide required a slightly larger dose, and it had to be given at more frequent intervals. The drug acted well in patients with recent as well as with old diabetes, obese or otherwise, and in diabetics above the age of 40. Rigid dietary control is, however, essential.

Vaginal Moniliasis.—S. C. Pandya and co-workers (*J. Indian M. A.* **30**:9 [May 1] 1958) studied the action of nystatin vaginal tablets in the treatment of 36 patients with vaginal moniliasis. The diagnosis was based on clinical evidence of vulvovaginitis, characteristic vaginal discharge, microscopic evidence of the presence of yeast cells in the discharge, and demonstration of Candida albicans in

the discharge. All the patients had a history of increasing vaginal discharge, which was of short duration in 19, present for over two months in nine, and present for over a year in 8. Thirty-four complained of itching around the anus, and 33 had burning on micturition. Six complained of a constant dull pain in the lower abdomen. Eight were nulliparas, 9 primiparas, and 19 multiparas. Twenty-four patients were receiving a nutritionally poor diet. The pH of the vaginal discharge was between 5 and 5.9 in 2 patients, between 6 and 6.9 in 30, and 7 in one. Thirty-two patients were treated with nystatin vaginal tablets. Half of them used one and the other half used two tablets at bedtime. One patient treated for six days with one tablet a day showed complete recovery during this period. Microscopically, the fungus could not be detected after the 12th day, and there was no relapse for at least nine weeks.

Twelve patients used one tablet a day for 8 to 14 days. Complete recovery resulted in all cases within 14 days, and microscopic evidence of cure was obtained between the 13th and 19th days. Of these, 10 patients did not relapse and the 2 who did responded to retreatment with nystatin. Five patients were treated with one tablet a day for 18 to 20 days. Complete clinical recovery occurred during this period, and cultures remained negative from the 20th day onwards. Fourteen patients used two tablets a day for one to two weeks. All were symptom-free in two weeks, and cultures were negative after the 14th to 20th day. No relapse occurred in 10 of these patients. Two patients received two tablets for 15 to 18 days each. Both were clinically cured, and cultures were negative after three weeks. There was no relapse. Thus best results were obtained with a treatment of about two weeks. The results also showed that treatment with one tablet a day was just as effective as with two tablets a day. The authors recommended the larger dosage in patients in whom the condition was severe or there were such complicating factors as diabetes or pregnancy. No change in the pH of the vaginal discharge was observed after successful treatment.

Electrophoretic Profile in Hematological Disorders.—V. B. Mitbander and co-workers (*Indian Journal of Medical Sciences*, vol. 12, Feb., 1958) studied the alterations in plasma proteins in 28 patients with hematological disorders. The plasma proteins were also determined in seven healthy adults between the ages 20 and 35 who served as controls. The percentages of α_1-globulin for the normal subjects were lower and those for V factor and fibrinogen higher than the percentages reported from other countries. A decrease in the albumin and β-globulin and an increase in the α_1-globulin were observed in patients with chronic granulocytic leukemia.

This is slightly different from the readings reported by other authors, who did not find any alteration in the albumin level. The decrease in the albumin in the present series may be due to the poorer nutritional status and hypoalbuminemia of these patients. In patients with chronic lymphocytic leukemia, the albumin level showed reduction while the α_1-globulin was increased. The other protein fractions showed individual variations. In a patient with anemia due to ancylostomiasis, the albumin level was lowered and all the globulin components were increased. In another patient with refractory anemia, all the plasma proteins were diminished except α_1-globulin, which remained constant. Similar changes were seen in patients with acquired hemolytic anemia. In other patients with anemia there was a marked increase in α-globulins, fibrinogen, and V factor and a decrease in the albumin. In a patient with miliary tuberculosis all the plasma proteins were diminished except α_1-globulin, the reduction being most marked in albumin.

In a patient with severe anemia with tuberculosis, albumin and β-globulin were decreased and other fractions were increased. α_1- and α_2-globulins were markedly increased in a patient with Hodgkin's disease; the albumin and β-globulins were decreased and the fibrinogen and the V factor increased. There was the characteristic hyperproteinemia in a patient with multiple myeloma, the Bence-Jones protein appearing in the V factor fraction; the fibrinogen showed a striking reduction, the albumin was decreased, α-globulin was elevated, and β-globulin unaffected. In all patients with visceral leishmaniases, an interesting pattern was seen with a marked increase in the V factor, a marked decrease in albumin, a decrease in β-globulin, and an increase in fibrinogen and α_1-globulin. The V factor showed a sharp increase in patients with chronic cirrhosis; the α-globulins were increased and albumin and β-globulin decreased. The pattern was normal in a patient with paroxysmal nocturnal hemoglobinuria, the total proteins also being unaffected. A marked increase in fibrinogen and V factor was seen in a patient with atypical reticulosis with hemolytic anemia in whom the Coombs test was repeatedly negative. Thus the changes as noticed in this series were characteristic in patients with Hodgkin's disease, multiple myeloma, visceral leishmaniasis, and cirrhosis while in leukemia, anemia, and tuberculosis they were nonspecific.

Psoralens for Vitiligo.—B. N. Srivastava (*Indian Journal of Dermatology and Venereology*, vol. 24, Jan.-March, 1958) gave methoxsalen orally and locally to 100 patients with vitiligo, their ages varying from 2½ months to 51 years. Most of the patients were vegetarians, and some showed definite evidence of malnutrition and vitamin deficiency;

24 had varying grades of anemia, mostly of the hypochromic microcytic type, and 26 had eosinophilia. In only one was there oxyuriasis. One patient had a family history of asthma, and another had eczema. In others no cause for the eosinophilia was apparent. The drug was given orally in a daily dose of 0.7 mg. per kilogram of body weight and externally in a lotion. On an average, the treatment was started in adults with 10 mg. per day in the first week, and the dose was increased by 10 mg. every week till 40 mg. a day was reached. This was continued till therapeutic results were obtained. If toxic reactions appeared, the dose was reduced or omitted temporarily. The dosage was modified in children according to their weight.

To minimize severe local reactions, local treatment was started with a 1:4 dilution of a paint containing 0.18% of methoxsalen. Sometimes higher dilutions with 60% alcohol as the solvent were used. An ointment was used instead of the lotion in sensitive patients. The paint was applied to the affected area at night, and the painted area was exposed to sunlight the next morning for about one minute initially and subsequently for one to five minutes. It was then washed thoroughly to prevent overexposure. In this series 28 patients were cured, and the rest showed some improvement. The minimum time taken for complete cure was three weeks and the maximum two years. Patients in the younger age group and those with vitiligo of recent origin responded earlier. In two patients the disease advanced in spite of treatment. Side-reactions included actinodermatitis, headache, anorexia, burning sensation, gastroenteritis, oral and rectal bleeding, anemia, urticaria, and psychotic episodes. Higher dilutions of the drug than those used by Western workers were found to be effective. Severe actinodermatitis resulted when a solution of a strength similar to that used in the West was used. The time required for the onset of pigmentation and cure was also comparatively shorter.

Drug Resistance in Bacillus Subtilis.—Joshi and Sreenivasan (*Proc. Indian Acad. Sc.* 47:1 [Jan., section B] 1958) stated that the acquisition of resistance to a drug may sometimes be due to the organism developing an ability to detoxify the drug, involving the synthesis of an enzyme which is concerned in the destruction of the drug. They studied local strains of Bacillus subtilis to find out whether organisms that have become resistant to sulfonamides owe this property to detoxification by acetylation through the mechanism of an enzyme. The organisms were exposed to concentrations of sulfanilamide gradually increasing to 500 mg. per 100 ml. in the culture medium. Sulfanilamide was used in these experiments because it is acetylated to a greater extent than *p*-aminobenzoic acid, sulfathiazole, or sulfadiazine. The extent of acetylation was studied with the susceptible parent strain as well as with strains that were rendered resistant to 50 and 500 mg. per 100 ml. of sulfanilamide. The susceptible strain gave a scanty growth in the presence of the drug, requiring a longer incubation period. With the resistant strain, good growth was seen within 18 hours. The free and total sulfanilamide was estimated in these cases at the end of 24 and 72 hours, but there was no evidence of acetylation. With strains resistant to higher concentrations of sulfanilamide, a diazotizable arylamine was produced in the culture filtrate in large quantities even in the absence of any added sulfanilamide. This amine was not seen in control tubes which were sterilized after inoculation and then incubated simultaneously for varying lengths of time. Thus the mechanism of detoxification of sulfonamides by acetylation is not the one involved in the production of drug resistance by B. subtilis.

MEXICO

Congress of Obstetrics and Gynecology.—At the joint meeting of the Latin American Congress of Obstetrics and Gynecology and the Mexican Congress of Obstetrics and Gynecology in Mexico City in June, H. Rocamora, of Cuba, reported on the surgical risk during pregnancy. In cesarean sections his case fatality rate dropped from 6.9% (1934 to 1940) to 0.6% (1948 to 1956) due mainly to the use of antibiotics, transfusions, better anesthesia, and simpler surgical techniques. Infections and hemorrhages cause 84% of the maternal deaths. Segmental transperitoneal cesarean section with the patient under spinal anesthesia is to be preferred. The case fatality rate in ectopic pregnancy was 1.2%. Of the surgical complications of pregnancy, appendicitis was most common. Appendectomy was not attended by a higher case fatality rate in pregnant than in nonpregnant women. In 66% of the patients with ovarian tumors it was necessary to interrupt pregnancy. Cardiovascular operations were performed successfully in two pregnant women. Surgical complications of pregnancy are rare in Cuba, and the speaker operates on such patients only when absolutely necessary.

A. de Moraes, of Brazil, discussed the treatment of advanced genital cancer in women. In selected cases extraradical surgery may produce fairly long survival periods and even five-year cures. Radium and x-ray therapy should be attempted in all inoperable patients. The radioisotopes, specially radioactive gold, can be useful and complement treatment with cobalt-60. Chemotherapy gives poor results in women with advanced genital cancer. As an adjunct to treatment, hormones, especially testosterone, can be helpful. Castration, hypophysectomy, and adrenalectomy do not cure cancer, and their value is doubtful. N. Dias B., of El Sal-

vador, reported a series of 1,485 patients with genital carcinoma; 1,318 of these had cervical carcinoma, 592 (44.9%) of which were advanced (stage 3 and 4). Extraradical surgery, radiation therapy, or a combination of both do not solve the problem of advanced genital carcinoma in women. Stage 3 cervical carcinoma should be treated primarily by radiation. Radical and extraradical surgery should be used only in selected cases or in the presence of radioresistance or recurrence. Irradiated patients should be kept under clinical, cytological, and histopathological observation to determine treatment in the later stages. Stage 4 carcinoma was treated by this speakers either by x-ray alone or by x-ray plus radium, with good palliative results. When there is involvement of the urinary bladder or the rectum, without fixation to the pelvis, an evisceration may be attempted. In the speaker's series, there were 38 cases of carcinoma of the vulva. Radical surgery in the operable patients showed that 50% had metastasis to pelvic lymph nodes, which indicates that vulvectomy should be accompanied not only by complete inguinal dissection but also by careful removal of the pelvic lymphatic system.

J. Noriega, of Mexico, stated that in his series, stage 3 carcinomas were treated with intrauterine radium and external irradiation, preferably with the cobalt bomb, aimed at the parametrial and lymphatic tissues. Stage 4 carcinomas were treated initially with external irradiation, with use of multiple small fields. According to the response, intrauterine radium might be applied. M. Briones P. and co-workers of Mexico discussed the physiopathological problems of the residual ovary. They concluded that ovaries should always be spared in young women, unless there is a clear indication for their removal. It is possible to save one or both ovaries, when they are healthy, and allow them an adequate blood supply, intact innervation, and good tubo-ovarian synergy. After 40 the incidence of tumors of the ovary increases. Although the incidence of such tumors may be as much as 21%, malignancy occurs in only 0.5%. Monthly checkups of women with residual ovaries are recommended for the first six months. After that checkups should be made at lengthening intervals, until they are made twice a year.

SWEDEN

Tissue Transplantations from the Dead.—With the growing practice of taking grafts from the skin, eyes, and bones of persons other than the recipients of them, the problem of ownership has come to the fore. The transfer is a comparatively simple matter from the legal aspect when both donor and recipient are alive, but surgeons have hesitated to help themselves to grafts from the dead when the transaction has not been legalized by some formal declaration on the subject from the prospective donor or his relatives. The parliament has now adopted legislation designed to facilitate the taking of grafts from the dead. The new law entitles certain hospital surgeons to help themselves to tissues taken from patients who have died in hospital or have been brought in dead. A safeguard against any abuse of this privilege is provided by a clause giving hospital patients or their nearest relatives the right to anticipate and prevent such action by forbidding it in advance.

State Mental Hospitals.—Debates in the Swedish Parliament continue to disclose the shortcomings of the state-managed mental hospitals which unfortunately do not share with Sweden's general hospitals in the reputation for being among the best in the world. More than a year ago, it was admitted in Parliament that in a mental hospital housing 669 patients there were only two attending physicians. Later figures covering the year 1956 showed that the average of overcrowding was 14%, though in certain hospitals it was 38%. In some of the older mental hospitals the patients must go to bed at 6 p. m. for want of personnel to look after them, and for want of proper lighting they cannot read in bed. Were funds available for new buildings to relieve the overcrowding, the lack of medical and subordinate staff would still be a serious obstacle, for over 63% of the junior hospital appointments are not filled or are held by temporary substitutes. A more optimistic note comes from the St. Lars hospital in Lund, where a locked wing for 65 violent women patients was thrown open and 39 patients are now engaged in occupational therapy thanks to the initiative of the medical superintendent and to modern drugs.

Specialization.—Of the 5,698 members of the Swedish Medical Association 3,318 have qualified as specialists. To enjoy the privileges conferred by specialization, they have had to fulfill various conditions before inclusion in the register kept for the purpose. Among the 26 different specialties there are several whose limitations are indicated by the paucity of exponents. Thus there are only six specialists in neurosurgery, six in disturbances of speech, and nine in plastic surgery. There are 21 in anesthesiology and 34 in diseases of the teeth. The most popular speciality is internal medicine with 783 qualified specialists. The surgeons and cardiologists come next with 491 and 264 respectively. Only 98 are neuropsychiatrists, whereas 222 are specialists in diseases of the lungs.

Influenza Epidemic.—Dr. Inga Rydén and coworkers (*Sevenka läkartidningen*, May 2, 1958) studied the outbreak of influenza that occurred in the fall of 1957. The epidemic showed no age or

sex discrimination, the number of patients over 70 corresponding to the age distribution of the whole population. Among the 85 patients admitted to hospital were 35 with pneumonia which usually ran a comparatively mild course, with the temperature returning to normal in three to four days. The virus of the Far East type A was isolated from eight patients who died and from others who recovered. A vaccine made from this type was given in two injections to the 24 members of the hospital staff likely to be exposed to massive infection in the course of their work as the epidemic progressed. Of these 14 remained well, 7 had a mild attack, and 3 had to report sick. The patients developing pneumonia were given antibiotics, and when penicillin or streptomycin failed, chloramphenicol was tried. None of the patients given chloramphenicol had to resort to any alternative antibiotic.

Kidney Stones and Gallstones.—Dr. A. Fritjofsson (*Nordisk medicin*, May 22, 1958) made a statistical analysis of the 20-year period 1937-1956 during which about 8,900 patients with stone in the kidneys and ureters were treated in the local hospitals. A chart of this period showed a fairly steady rise in the number of such cases, but to discount the confusion due to the growth of the population, the figures were readjusted so as to present the number of these cases per 100,000 of the population. With this readjustment there was a rise from 460 in the first five years to 900 in the last five. Fritjofsson then quoted the findings of Edlund and Olsson who in 1956 published a study of the cholecystectomies carried out in Gothenburg during the 15-year period 1940-1954. They also took the precaution to calculate their numbers per 100,000 inhabitants and found that these numbers had more than tripled in 15 years. The reasons for these increases remain obscure.

Hospital Administration.—In recent planning for prospective hospital legislation, it was proposed that laymen should be put in charge of hospital administration on the assumption that in this respect they are more effective than members of the medical profession. This proposition led to a meeting last December at which the Swedish Medical Association and other bodies interested in hospital services were represented. It was agreed that medical administration was preferable to lay administration of such services and that it was desirable for doctors willing to discharge administrative hospital duties to qualify for them by special training. To this end it was agreed that such training should be made available for up to 20 trainees in May. The Swedish Medical Association has undertaken to contribute to the expenses of these trainees whose attendance at the short course of lectures in May may be supplemented later by a much more ambitious course of several weeks. This latest move is just one more protest against the teaching that medical men are unsuited by their training for administrative responsibility. To counter it effectively, the Swedish holders of senior hospital appointments are urged in the organ of the Swedish Medical Association not to trust to improvisation when taking on administrative duties, but to fit themselves for them by the educational facilities now available.

UNITED KINGDOM

Medical Ethics.—The General Medical Council is sending every physician a notice, reminding him of the major rules of his profession and the penalties for breaking them. The existing rules had not been amended since 1914, and as a result many physicians appear before the disciplinary committee of the council on charges not mentioned in the present notice. The new notice sets out offenses which raise questions of infamous conduct under the following main headings: (1) adultery, or improper conduct with a patient; (2) advertising and canvassing; (3) signing untrue or misleading certificates; (4) associating with unqualified practitioners, such as faith-healers; and (5) miscellaneous other items. Some members of the council have been worried about the increase in the number of physicians charged with offenses involving alcohol and at some trends in the issuing of medical certificates. The appearance of doctors on television has raised complex questions about advertising.

Assessment of Drug Action.—A symposium on quantitative methods in human pharmacology and therapeutics was held in the Wellcome Auditorium, London, in March. It was arranged by the coordinating Committee for Symposia on Drug Action of the Biological Council and was supported by the British Pharmacological Society, the Royal Society of Medicine, the Physiological Society, and the Biometric and Nutrition Society. In the session on the measurement of subjective states Prof. C. A. Keele said that the best way to measure pain and compare the effects of analgesic drugs was to rely on subjective assessments by the patient rather than to attempt to measure such physical accompaniments of pain as sweating, change in pulse rate, and wincing, as these are too variable. Dr. P. Sainsbury told how, by electromyography, he measured muscle tone, involuntary movements, fidgeting, and gestures in anxious patients as an index of anxiety.

Dr. H. Steinberg discussed the quantitative effect of drugs on intellectual performance, reasoning, memory, perception, and vigilance. The effect of drugs on performance may be either on incentive or on the actual ability to do the job. It is important to distinguish between the two. Drug re-

sponses may vary according to whether a subject knows whether he is doing well or badly in a test. Small degrees of anxiety act as an incentive, and it may be important that this should not be suppressed by drugs, or achievement may be hindered. Fortunately this problem is not socially urgent, as drugs are relatively ineffective in allaying anxiety without producing undesirable side-effects. The symposium was reported in the *British Medical Journal* for May 3.

Symposium on Clinical Trials.—A symposium on clinical trials was held at the Royal Society of Medicine (*British Medical Journal*, May 3, 1958). Dr. J. G. Scadding said one prerequisite was that extensive experiments on animals, and, sometimes, a few human volunteers had been carried out. A pilot trial might follow, and then a controlled trial. In some circumstances ethics would always make a therapeutic trial impermissible, because at all times the patient should be given the advantage of the best treatment available. Professor J. W. Crofton, after saying that the control group was in many respects the safest one to belong to, pointed out that in some situations no control group was required. This might be so during the testing of the treatment of a highly fatal acute disease, such as tuberculous meningitis with streptomycin, or the testing of a new drug with consistently dramatic results, such as chloramphenicol in scrub typhus. The physician taking part in the trial must have a "conscience clause" so that he can give his patient the best possible treatment regardless, if necessary, of the trial's requirements. Thus the results of treatment with many familiar substances are still not precisely known. Dr. Dudley Hart dwelt on the dangers of enthusiasm in the staff concerned in a therapeutic trial and showed how a "revivalist" atmosphere surrounding the introduction of a new method of treatment could not merely upset the recording of observations and the deductions to be made from them but could lead to the production of entirely misleading data by patients whose reactions to treatment sprang from a strong expectation of cure. Among the rules he set out for the careful control of a trial were: "Be disinterested," and "Consult a statistician beforehand."

Renal Damage by Mercurial Diuretics.—Mercurial diuretics are often given to patients with congestive heart failure irrespective of the state of the kidneys. Five cases of the nephrotic syndrome attributed to the use of mercurial diuretics over long periods were observed by Riddle and coworkers (*Brit. M. J.* 1:1274, 1958) who concluded that the syndrome is a definite risk in long-term mercurial diuretic therapy and that it may be more frequent than has hitherto been supposed. The diuretics used were mersalyl, Neptal chlormerodrin, and mercaptomerin. Two of the patients received weekly injections of mersalyl for three years. Three patients died, and although there was no previous history of renal disease, the clinical features and pathological findings were consistent with a nephrotoxic action of mercury. The urine was loaded with protein, the serum albumin level was low, and the serum cholesterol level raised. In the three fatal cases the macroscopic and microscopic appearance of the kidneys was the same. The cortices were swollen and were pale yellow-gray. The renal tubules showed necrosis, degeneration of the epithelium, and infiltration of the tubular cells with isotropic and anisotropic fat. Elsewhere cloudy swelling and hyaline droplet degeneration were observed. Tests for mercury in the kidney were strongly positive. The pathological changes resembled those seen in mercury poisoning. Increasing edema and increasing dyspnea were mistaken for a terminal exacerbation of chronic heart failure but were due to renal failure. Treatment with dimercaprol, corticotropin, and ion-exchange resins was of no avail. One patient recovered without specific therapy, suggesting that the condition is sometimes reversible. Early recognition of the condition and cessation of mercurial therapy before irreparable renal damage has occurred offers the best chance of recovery. The warning signs of the onset of the nephrotic syndrome are failure of proteinuria to decrease after a satisfactory diuresis, increasing edema, and absence of diuresis after injections of a mercurial diuretic. The first is the most useful sign.

Shoe-Fitting Fluoroscopes.—As a result of an agreement between the manufacturers of shoe-fitting fluoroscopes, the retail shoe trade, and the home office, the amount of radiation emitted by these machines was limited as of July 1. Each fluoroscope must bear a notice on it warning against over exposure, and existing machines that do not conform to regulations and emit more than the allowable degree of radiation must be modified. A notice on the machines will advise customers buying shoes not to have more than 12 shoe-fitting exposures a year. Operators trained in using them will see that each exposure is minimal. This approach by the manufacturers was prompted by a recent report by the Medical Research Council, which urged that the use of x-rays in shoe-fitting be abandoned except when necessary for orthopedic reasons.

Tetanus.—At a meeting at the Royal Society of Medicine, Professor Payling Wright of London explained how tracer techniques using labeled foreign proteins and fluorescent dyes enabled the fate of an injection of antitetanic serum (A. T. S.) to be followed. Such foreign proteins as tetanus-antitoxic horse globulins are removed from the circulation and destroyed more rapidly after the second

or subsequent inoculation. The first dose of 1,500 units of A. T. S. confers protection for two or three weeks, but tracer studies show that the second dose disappears in a much shorter time. Professor Wright cited a case of tetanus occurring after the usual prophylactic dose of A. T. S. and recommended immunization against diphtheria and tetanus with the appropriate toxoid. Once a person has been injected with horse serum proteins, A. T. S. cannot be guaranteed to protect against tetanus, should exposure occur. Dr. D. Laurence deprecated the treatment of tetanus with drugs of unknown activity. Ideally any remedy should prevent spasms without blocking respiration or consciousness. Muscle spasms are best relieved by chlorpromazine and related compounds, which are better than muscle relaxants and centrally acting relaxants such as mephenesin. The best compound tested was acetylpromazine, although it has not been submitted to clinical trial yet. Relief of anxiety is essential in the management of tetanus.

Professor E. Adams, of Durban, reported a controlled clinical trial of chlorpromazine in nearly 200 patients with tetanus. His impression was that a mixture of barbiturates and chlorpromazine was better than either drug alone and enabled smaller doses of each to be given. In neonatal tetanus he preferred barbiturates. Chlorpromazine could be given intravenously and was of help in controlling laryngeal spasm. The total daily dose should not exceed 1 Gm. In assessing any new form of treatment, such prognostic criteria as period of onset and severity of spasms must be considered in each case. The earlier the onset the higher the mortality, and the less severe the spasms the lower the mortality. The cause of death is variable, but exhaustion from spasms is not a likely cause. Respiratory complications, hyperpyrexia, and circulatory failure are far more likely. Dr. A. C. Smith, of Oxford, said that new methods of treating tetanus had little effect in reducing mortality. At the Oxford Respiration Unit patients with spasms that could not be controlled by other means were given muscle relaxants and intermittent-pressure respiration. Four of seven recovered completely. Such a technique can only be carried out in specially equipped centers. Careful nursing and biochemical control are essential. This form of treatment could be carried out for three or four weeks if necessary.

Prognosis of Infectious Hepatitis.—Although it is generally agreed that most patients suffering from acute infectious hepatitis recover completely, with no lasting damage to the liver, few long-term follow-up studies had been made to confirm this impression. Cullinan and co-workers (*Brit. M. J.* 1:1315, 1958) followed up 1,405 men who had suffered from this disease in one of the four massive outbreaks of the disease that ravaged the armies massed around the Mediterranean Sea in World War II. Infectious hepatitis cost the British troops in the Middle East over 500,000 man-days in hospital. Most of the men were between the ages of 18 and 30 years, and the incidence in the officers was much greater than in men of other ranks. There were only four deaths from hepatic necrosis associated with the acute attack, a case fatality rate of 0.28%. Of the original 1,405 men, 91.6% were contacted. Recurrence of symptoms occurred in 8.3% of patients after leaving hospital at times varying from weeks to several years. About 26% felt completely fit immediately after leaving hospital: 68% at the end of a month, 87% at the end of three months, and 95% at the end of one year. The general pattern of illness in those who were not fit was one of malaise and digestive disturbance. Seven years after the attack 3.2% of the men complained that they had not felt well since the acute illness. They complained of periodic slight jaundice, persistent lassitude, intolerance of fat and alcohol, loss of appetite, nausea, depression, indigestion, and periodic vomiting. No deaths after the original illness and no cases of subacute necrosis leading to cirrhosis were recorded.

Factory Work in Mental Hospitals.—The Minister of Health and his staff are discussing ways of introducing industrial work in mental hospitals in order to accelerate the social rehabilitation of the patients. This followed a suggestion made by the Central Health Services Council in their annual report. The Medical Research Council has already set up workshops in mental hospitals, where selected patients have been given work contracted from neighboring factories. Schemes have been developed in 13 mental hospitals and 8 mental deficiency hospitals, with marked psychiatric and social benefit to the patients. The council's report recommends that the industrial projects in the hospitals be separate units, with normal working hours and conditions and standard factory pay rates. Working under conditions similar to those in industry should give the patients an incentive to reestablish themselves socially and encouragement to handle their own money and so regain the habit of looking after themselves.

Shortage of X-ray Technicians.—There is such a shortage of x-ray technicians at Walsall Hospital that two of them are having daily blood examinations because of the risk they run of excessive exposure to radiation. At an inquest on an elderly woman who died at the hospital while undergoing an emergency operation, it was stated that it was not possible to obtain an x-ray examination at the time owing to shortage of staff. Due to understaffing these technicians were overworked. The shortage is attributed to the long training required and the low salaries paid. A newly qualified technician receives $1,200 to $1,300 a year, with the expectation of a maximum of $1,600. The shortage is most acute in the smaller hospitals.

Death of Webb-Johnson.—Lord Webb-Johnson, former president of the Royal College of Surgeons and consulting surgeon to the Middlesex Hospital, died in London at the age of 77. When Dean of the Middlesex Hospital Medical School in the 1930's he was largely responsible for the rebuilding of the Middlesex Hospital. Great damage was done to the buildings of the Royal College of Surgeons in London in World War II, and during Lord Webb-Johnson's presidency of the college he was instrumental in expediting the rebuilding. New departments were established and professorial chairs were endowed for anatomy, pathology, and ophthalmology, and faculties in dental surgery and anesthesiology were established. In this he was helped by funds provided by Lord Nuffield, The Wellcome Trust, and a former patient.

Spiritual Healing.—Following swiftly on the heels of its counterpart in Scotland, as reported previously, the Church of England has published a report on spiritual healing. In this the view is expressed that the time is ripe for a *rapprochement* between the church and medicine. Medical science is laying increased emphasis on the unity of man's nature, recognizing more and more that the causes of much physical illness and mental disturbance are to be found in the deep and intimate relationship of the physical, mental, moral, and spiritual in man. In discussing public healing services, the report sees dangers inherent in large public demonstrations of healing and considers that these dangers are present even in the smaller and more carefully controlled public healing services held in parishes. It is recommended that in every diocese a panel of priests and physicians be set up under the authority of the bishops to advise the clergy in matters relating to the conduct of healing services. Further the clergy should do their utmost to secure the understanding, advice, and cooperation of the medical attendants of those to whom they minister. Persons seeking the ministrations of the church at a healing service should be advised to place themselves under the care of a physician if they have not already done so. The report commends to the attention of principals of theological colleges, deans of medical schools, and chaplains of teaching hospitals the recommendation of the British Medical Association, that the purpose of cooperation between the physician and the clergyman should be brought before medical and theological students by means of lectures and discussions.

On the subject of demonology, it was found that some form of exorcism is at present used in this country: infrequently in the case of persons, but less infrequently in the case of places. The great difficulty in detecting demons is stressed, and also the dangers inherent in the misuse of exorcism. The patient must therefore be carefully examined, both medically and spiritually, the physician and the priest working in close collaboration. The archbishops are asked to consult with the appropriate medical authorities with a view to setting up an advisory panel consisting of priests and physicians, and it is recommended that exorcism should be practiced only with the authority of the diocesan bishop after he has consulted with this advisory panel.

Radiotherapy in Carcinoma of the Lung.—In a series of 347 patients with inoperable bronchogenic carcinoma 200 were treated by radiotherapy. The results were analyzed by K. Sicher (*Practitioner* **180**:695, 1958). Symptomatic relief was about the same, irrespective of the dosage used. About 70% of patients obtained excellent or good relief, but the percentage of objective improvements was higher among those treated with elaborate techniques and a larger dose, and these patients also had a better survival rate. Of 23 patients who survived a year or more, 16 received more than 4,000 r. The difference in survival time between treated and untreated patients was statistically significant: 11.5% of the former were alive after one year, compared with only 2% of the latter, and after three years 4.5% of the treated patients were still alive but none of the untreated. As most of the patients were in an advanced stage of the disease, a survival rate of 4.5% for three years is noteworthy. Those who survived longer after treatment also enjoyed symptomatic relief, and therefore their lives were really worth prolonging. The policy adopted in this department as a result of this survey is that every patient with an inoperable bronchogenic tumor be given the benefit of radiotherapy, unless the expectation of life is thought to be less than one month. Even in some of these unfortunate patients a short course of deep x-ray therapy is helpful if severe respiratory symptoms are present.

Ultrasonic Diagnosis.—The use of the echo patterns obtained by pulsed ultrasound in the diagnosis of large intra-abdominal masses, including the gravid uterus, pelvic tumors, and ascites, was investigated by Ian Donald and co-workers (*Lancet* **1**:1188, 1958). Masses containing fluid were easily but crudely demonstrated. Their experience of 78 patients in whom diagnosis was quickly verified by laparotomy and subsequent histology indicated that ultrasonic diagnosis is still crude and that the preoperative diagnosis of histological structure is still far off. Their most interesting patient was one in whom the clinical diagnosis was convincingly that of a uterine fibroid, but ultrasonic scanning revealed a fetus in the uterus, and the diagnosis of pregnancy was subsequently confirmed. On the basis of experiments with newborn kittens, it was concluded that exposure of the kittens to more than 30 times the dose of ultrasound necessary in its diagnostic use produced no detectable neurological changes.

LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Sherman Anti-Trust Act: Practice of Medicine as Interstate Commerce.—This was an action for treble damages for violations of the Sherman Anti-Trust Act because of the allegedly wrongful refusal of the defendant society to admit the plaintiff as a member. From a judgment in favor of the defendant, the plaintiff appealed to the United States court of appeals for the eighth circuit.

The plaintiff was a licensed physician and surgeon and had been practicing his profession in Washington County, Arkansas, since 1935. He alleged that in the course of his practice he received, accepted, treated, and administered to patients from Arkansas, Oklahoma, Kansas, Missouri, Texas, and other states and that he would have had many more patients from those, and other, states if he had been permitted to become a member of the Washington County Medical Society. He had applied for membership four times but had been rejected each time, and he alleged that the defendants had combined and conspired among themselves not to admit him to membership in the society. This, he alleged, was a violation of the Sherman Anti-Trust Act.

The defendant contended that the Sherman Act was not applicable to the facts set forth in the plaintiff's complaint and that the court was therefore without jurisdiction to hear the case. It is to be noted, said the court of appeals, that the complaint is confined to the plaintiff's private medical practice. It charges no economic burden on the public by reason of the alleged acts of the defendants. There is no charge that the rejection of the plaintiff's application for membership in the Washington County Medical Society resulted in the raising or fixing of fees charged the public by other physicians. There is no allegation in the complaint remotely suggesting that the acts of the defendants cast any burden on interstate commerce. The mere fact that the plaintiff, at his location in Arkansas, may be treating patients from other states who must travel interstate does not result in his practicing his profession in interstate commerce, as the transportation of such patients is incidental. The practice of his profession, as disclosed by the allegations of his complaint, is neither trade nor commerce within Section 1 of the Sherman Anti-Trust Act. The plaintiff has not been prevented from practicing his profession, but in the final analysis his complaint is that he could practice it more profitably but for the acts of the defendants. The Sherman Anti-Trust Act was not primarily to protect the individual but to protect the general public economically, and a private party may not recover under the act unless there has been an injury to the general public economically.

The court of appeals pointed out that a prior decision had held that the practice of medicine, as conducted within the State of Oregon by doctors of Oregon, is not trade or commerce within the meaning of Section 1 of the Sherman Act. This was affirmed by the Supreme Court of the United States. In another case, the court held that the practice of the healing arts in Colorado is wholly local in character. "The mere fact," said the court in that case, "that a fortuitous and incidental effect of such conspiracy and acts may be to reduce the number of persons who will come from other states and countries to the Spears Hospital for chiropractic treatments does not create such a relation between interstate and foreign commerce and such local activities as to make them a part of such commerce."

In conclusion, the court of appeals said that the plaintiff's complaint is, in effect, that the practice of his profession would have been more profitable to him had the defendants not deprived him of membership in the Washington County Medical Society. The plaintiff was not prevented from practicing his profession, and the complaint is wholly lacking in allegations essential to a cause of action under the Sherman Anti-Trust Act. The judgment in favor of the defendants was therefore affirmed. *Rigall v. Washington County Medical Society, et al.*, 249 F(2) 266.

THE LEISURE CORNER

PLAYING HANDBALL

Handball requires a great deal of stamina, and for that reason many doctors enjoy batting around a rubber ball with a light leather glove. Handball is Irish in origin and a thousand years old. Robert Ripley, the "Believe It Or Not" man, who himself was an ardent enthusiast of the game, claimed that it was the oldest of all games played with a ball. Today, handball is played more often on this continent than anywhere else in the world. About 1850, William Baggs of Tipperary developed the first scientific method for playing the game. He made extensive tours in the United States, coaching and defeating all opponents. He originated new ways of striking the ball so that it would hop or stay close to the floor surface.

Although the rules governing the old and the new versions of handball are very much the same, two important factors, the ball and the court, are quite different. The old-time hard ball suggested a miniature baseball. It had a tight horse-hide covering and was sewn like a baseball, with a center of cork and tightly wound with strips of crude rubber and thread or yarn. The use of this type of hard ball required large, wide courts. Unlike the modern game, kicking was permitted and players were quite adept at returning particularly low balls with their feet.

The adoption and standardization of the soft ball game began during the 1890's when a new ball, about the size of our present day tennis ball, put in an appearance on handball courts in New York City. When players started to use this new type of soft ball, they found that it was not lively enough and that the game was too slow. However, what the soft ball innovation actually did accomplish was to popularize handball among men, boys, and girls. Hitting a ball against a brick wall of a building spread the popularity of the game from coast to coast.

All of this led to the downfall of the hard ball game. The change in the type of ball used produced a new method of playing handball. It was then called single-wall handball and was now strictly an American game. Its growth has been more rapid than the four-wall game chiefly for two reasons. First, playing facilities became more readily available, for it was now possible to play against any smooth surface. Secondly, it was possible to set up more adequate spectator accommodations by constructing bleachers on three sides of the court.

Many doctors are in need of some type of recreational physical activity. It is often advisable for them to have some form of exercise which is conducive to good health and provides mental relaxation. For the older man, handball is a wholesome and invigorating diversion that can be played leisurely without a great amount of effort. Coordination of all parts of the body is developed, and the desire for improving one's game always provides a challenge. There are few games which require so great an amount of scientific play, where quick choices are presented and split-second decisions have to be made. Any doctor can learn to play the game in a relatively short time and enjoy harvesting some of the physical benefits derived from a 45-minute workout. In fact, many players have found it is possible to obtain all the exercise they need in a shorter time. They usually play on indoor courts, and the weather does not alter their activity. The opportunity to use both hands in a like manner is another distinct advantage of handball over other games. This factor is particularly important, as it develops better all-round postural habits. Aside from the conditioning value of the game, is the need for coordination between eye and body movement that is exceedingly stimulating to anyone who plays. Handball is one of the least expensive of all the sports, as the initial outlay is the price of a pair of gloves and a ball. If necessary, any pair of old leather gloves can be used.

For the beginner it is better that he play by himself the first few times on the court, practicing each shot until he has mastered the fundamentals of play. For the first few times it is good practice to throw the ball so that it comes off the wall at different angles. As you continue to play you will learn to anticipate the position you have to take in order to make a good return shot; this saves many steps and results in a more scientific play. The person new at the game should concentrate on the underhand stroke, especially with his weaker hand. The ball should be played as low as possible in the beginning, with the player constantly attempting to be in position for the next shot.

It is interesting to note how a game of handball has the faculty to bring out both good and bad qualities of a person. Handball is usually played without the service of a referee, except perhaps in tournament play. There is an opportunity for blocking, shoving, and an occasional push. When these take place the activity loses its enjoyment, and the sport ceases to be a game of skill. It is therefore helpful to be fully aware of the few court procedures so that no embarrassing moments will alter the pleasure of the game.

For instance, do not cross in front of the ball, thereby obstructing your opponent's view, but allow him a fair opportunity to make his return shot. When playing on a warm day, try to keep the ball as free from perspiration as possible, since there is little pleasure in playing with a ball that slides along the wall in a different manner each time it strikes. If a play is questionable, it is customary to play the rally over. (A ball striking the front wall close to the floor is good if it comes out fairly straight. If it comes up, it has hit the floor first, hence, bad.) Should your opponent call a "hinder," it is usually good form to accept the decision without further consideration. The theory behind handball strategy is the same as that behind most sports, namely, placing the ball out of the reach of your opponent. After the rudiments of the game are mastered, and the player is able to devote his time and energy to out-guessing his opponent, the game

picks up a thrill with every shot. The most common method of hitting the ball is with the hand in a semi-cupped position, with the fingers slightly close together. The ball strikes the cushion portion of the hand at the base of the fingers, but depending on the stroke of the arm, the ball may slide off between the thumb and forefinger.

At Columbia University, handball is a highly regarded game; it is included as one of the three recreational physical education activities required of every student. It is taught in small groups of from 10 to 25 students. Many colleges have a "sports library" for students interested in the game. An occasional demonstration by outstanding players throughout the course is of value to the novice player from the standpoint of motivating and learning. Many Y. M. C. A.'s have programs of instruction and playing, and these are available to busy doctors.

MISCELLANY

ELECTRONICS AND BIOLOGY

David Sarnoff, New York

Because of its amazing versatility, electronics has had an impact on virtually every aspect of human existence. That includes the field of health and healment, where electronics already has made some significant contributions and where its potentialities for the future seem even greater.

Kinship of Electronics and Biology

The more we explore their relationships, the more impressed we become by the kinship of electronics and biology. Both depend heavily on physics and chemistry and present phenomena which can be grasped only when the structure of the atoms, and the forces within and between them, are understood. Increasingly each of them depends on a close study of the solid, liquid, and gaseous states of matter.

But the kinship goes much deeper. Perhaps the most significant clue to their affinity is that electronics and biology alike place basic emphasis upon minute component elements, the so-called elementary particles.

In the past, man concentrated attention on massive entities and their gross or general form. In the electrical field, the primary concern was with big motors and generators, large conductors, and the like. In biology, interest was directed to the visible and tangible parts of the living organism. Structure held the center of the stage.

But, in recent years, we have seen a radical shift of emphasis to the tiniest particles—the invisible building blocks of the universe. The infinitesimal has been recognized as the most potent and controlling aspect of nature. We in electronics work with the atom and its nucleus, with electrons, protons, neutrons, ions. You in biology study bacteria, viruses, the gene, the cell, and the still smaller building blocks—the complex molecules of biochemistry.

That meaningful parallel is reflected in the guiding principles, methods and insights, trends and scope of inquiry which are common to both fields. What is more, as our tools of investigation are further sharpened, the present strong resemblances portend discoveries which may reveal actual identity.

Man as a Communication System

Another analogy, one that I find endlessly fascinating, is packed with rich promise for both our sciences. I refer to the fact that communication theory (which is at the heart of many electronic systems) applies also to human beings. The degree of similarity is really astonishing.

About 70 years ago, a French physicist, Edouard Branly, was testing different theories as to how nerves carry messages from the skin to the brain and back again. He noted that the nerves are not continuous fibers but are formed of neurons and synapses, closely massed but not necessarily in contact. Applying this discovery to electromagnetic or radio waves, he found to his own amazement that a similar principle held good. The first successful detector of radio waves, the Branly detector, was thus the result of observations in the biological area.

Branly's intuition was merely a beginning. Since then it has been demonstrated that the physiological message-carrying system is the archetype of what the electronic engineer seeks to duplicate.

In order to form an integrated functioning unit, man's trillions of cells must be electrically and electrochemically interconnected. This "intercom" system consists of groups that operate concurrently in what we in electronics call a "multiplex system." The connective channels, or neurons and secretions, work both inwardly and outwardly. Inwardly, they carry impressions from the sense organ to corresponding cells within the central nervous system in the brain and spinal cord. Outwardly, they con-

Chairman of the Board, Radio Corporation of America.

Read before the World Congress of Gastroenterology, Washington, D. C., May 25, 1958.

trol muscles, glands, and other body elements. They function to coordinate messages from one part of the body to another. Additional channels continually report back to the brain the extent to which a willed act is being performed, and associated brain cells initiate and control any needed corrective action. In electronics, this is the familiar principle of "feedback."

This marvelous communication system inside man makes the most elaborate outside communication system elementary by comparison. Yet the underlying parallels between the body's communication system and that of electronic equipment—in the most advanced computer or "electronic brain," for instance—are remarkable. They challenge our imagination.

Contributions of Electronics to Biology

Already the impact of electronics upon biology, medicine, and related disciplines is far greater than many practitioners, let alone the public, realize. A great array of electronic tools and techniques is today in use or available for use by physician and surgeon, anesthetist, and radiologist. And even more promising devices are now in various stages of gestation in electronic laboratories.

Literally every electronic advance for communication or industry yields new knowledge, enabling readier access to hitherto impenetrable recesses and aspects of the human body and the production of more effective instrumentalities for medical and surgical practice.

Television, for instance, is thought of primarily as a mass medium of information and entertainment. Yet closed-circuit TV, both in black-and-white and in color, is becoming a vital adjunct to medical education. Electronic computers, to cite another instance, are thought of primarily in relation to industry and business. Yet their capabilities are multiplying the effectiveness of every man and woman engaged in biological and medical research.

The researcher in biology and the diagnostician in medicine depend largely upon the tools at their disposal. They need electromechanical, electrochemical, and electrothermal equipment; acoustic devices; high-speed apparatus for measuring, recording, and analyzing data; methods of high magnification.

In all these respects, electronics is increasingly at their service. It can relieve the professional worker from many routine tasks by collecting and processing information automatically, instantaneously, and with unprecedented accuracy. Electronic devices can perform jobs involving differentiation between similar objects. They can count them in a given area, record and store the resulting data, make them instantly available when needed, and compute the degrees of their correspondence or difference.

One of the major contributions of electronics is by this time fairly familiar: the electron microscope, which surpasses the capacity of the optical microscope at least 100-fold. Of immense importance in chemistry, metallurgy, and other industrial fields, it is equally if not more valuable to the biological and medical worker.

Then there is the electronic stethoscope, which picks up heart sounds, chest vibrations, or sounds from other organs and amplifies them accurately for a telephone headset or loud-speaker. It yields far more information than the conventional stethoscope. Recently a capacitance pick-up has been developed for the study of heart sounds and the early detection of heart defects.

Today blood pressure and spinal fluid pressure can be measured electronically and indicated directly. The same is true with respect to currents generated within the brain. New electronic tools promise significant expansion and refinement of present methods of electroencephalography.

At the research end, the so-called alpha and other rhythms in brain-generated electricity have been studied for as many as 50,000 samples obtained and recorded in three minutes, then promptly analyzed by electronic means. Unquestionably, electronic techniques can be expected to yield an enormous new understanding of the brain, ultimately helping to solve some types of mental disorders and some brain tumor problems.

Similarly the principles of radar and sonar, so vital to national security, have found valuable applications in diagnostic medicine. Sonic and ultrasonic vibrations are focused on the bodily area under examination. When they strike internal structures, they are absorbed or reflected. The reflections are systematically detected and the location of an obstruction exactly charted. Unlike x-rays, ultrasonic beams can detect cysts and growths which differ in structure, but not necessarily in density or effective atomic weight, from the surrounding mass.

Electronics is of increasing importance, also, to the radiologist. He has always contended with the risks of physiological damage where prolonged exposure is necessary. One solution of this problem has been found in electronic methods of amplifying the brightness of the picture, thereby permitting a smaller x-ray dosage. It is also proving possible electronically to sharpen the edges and the contrast

in x-ray pictures and to improve stereoscopic pictures, those taken from a number of viewing angles simultaneously.

Electronics also permits the direct study of organic specimens with another kind of invisible radiation, the ultraviolet. While unstained cells are commonly uniformly transparent in the visible, their component parts exhibit sharply differentiated absorptions in the ultraviolet spectrum. The newly developed ultraviolet color-translating television microscope employs a modified color television technique to translate differences in ultraviolet absorption into visible color differences. With its aid, natural tissues yield color pictures revealing at a glance the distribution of important chemical constituents in the cell. The great promise of the method for fundamental biological research is obvious.

Dr. Vladimir Zworykin and his colleagues recently have produced a startling instrument that has come to be called a radio pill—a miniscule radio transmitter which can actually be swallowed. Because the frequency of its signals is governed by the variations of pressures on the capsule, a receiver outside the body gathers telltale information from inside the stomach.

Without doubt this boldly conceived device represents a breakthrough in biological research and diagnostics, since it is the forerunner of a multitude of coming adaptations. They should enable us to study various conditions in the body with a minimum of surgery and, in some cases, without recourse to surgery. At other times they will provide the diagnostic data that, when surgery is indicated, will make it more accurate.

Artificial Bodily Organs

The surgeon, in fact, has a particularly large stake in enlisting the electron in his service. The most spectacular development in this area is electronic mechanisms acting as temporary substitute organs in the human body while the natural organ is being worked upon. That a man-made device could ever, however briefly, take over the functions of a bodily organ would have seemed wildly improbable before the electronic age. But to a limited extent this goal has already been reached, bringing within the bounds of feasible surgery some operations formerly considered imprudent, if not impossible.

The most dramatic of the substitute organs is the artificial heart. Here we have an electrically driven and electronically controlled device which bypasses blood flow around the heart and carries out the normal effects of the heart beat while maintaining a pace adjusted to the needs of the patient. When one reflects that the blood must not clot within the artificial heart, that temperatures and pressures must be maintained with the utmost precision, it is clear that here we have a case where medical science is stranger than science-fiction.

Paralleling the artificial heart, we have the development of an artificial lung and an artificial kidney, each bypassing the natural organ while it is being examined or repaired, each made possible by electronic sensing and control devices.

Inevitably one wonders whether the use of these artificial organs need forever be restricted to the operating room. In theory, at least, it is conceivable that one day compact electronic substitutes will be provided on a permanent basis to replace organs that have become defective through injury or age.

Artificial kidneys, lungs, and even hearts may then become as familiar as artificial teeth or hearing aids. Indeed, one may imagine a man walking around in apparent good health with several of his organs replaced by the refined electronic substitutes of the future. Admittedly the idea is fantastic, but, as the marvels of electronics unfold, the line between fantasy and fact is ever harder to define.

In the field of orthopedics, electronic methods are not yet at the point of major utility but important possibilities are in evidence. Electronic apparatus for systematic and automatic exercise of any part of the body—in cases of partial paralysis, for instance—are already far advanced.

More important, electronics promises sensational improvement of prosthetic devices. At the heart of this promise is the electronic capacity to amplify the minutest muscular efforts and impulses to almost any desired magnitude. The outlook—though as yet only a hope—is for equipment which, attached to the stumps of an amputated limb or to some other part of the anatomy, will actuate and control movements of an artificial leg, arm, or even fingers with acceptable precision.

For the nearly deaf, the bone-conduction receivers or compact electronic equipment for large audio amplification now in use are being constantly improved, and other expedients under study show encouraging prospects.

Among the most humanly exciting potentials now at the experimental stage are devices that in some measure "see" for the blind. Interesting beginnings have been made, for example, toward electronic detection of obstacles in the path of the blind or sudden changes in the ground or pavement levels. Progress is being registered, too, in

electronic equipment for translating ordinary type into audible signals, thus enabling the blind to "read" conventional printed matter.

This inventory of the electronic contribution to biology, medicine, and surgery is far from complete, of course. Every piece of new equipment, it should be remembered, tends to become the progenitor of a whole family of devices, each adapted to additional uses as it is refined to meet more complex conditions.

The same principles of energy under precise controls which, at one extreme, guide a man-made satellite into an orbit around our planet are applied, at the other extreme, to arm the biological professions with unprecedented instrumentalities for the pursuit of their specialized knowledge and the healment of human beings.

Color Television and Biology

Anything that the human eye can see can be transmitted by television in true color. This truth has endless implications for everyone directly or indirectly engaged in the alleviation of bodily suffering. The horizons opened up are so wide that I need only mention a few to suggest their magnitude.

The details of an operation or the appearance of a lesion can now be sent to any desired point for examination. Any malfunctioning area can be studied without the examiner actually visiting the patient. We can envisage a time when the individual patient, in a hospital or at home, can be viewed and advised by a physician from any distance. Microscopic slides and x-ray pictures can be studied at places remote from their physical location. Any picture in motion—let us say of an operation in progress—can be viewed directly, in normal size or greatly enlarged, at any desired point of reception.

Panels of specialists hundreds or thousands of miles apart can consult about a case. Fully illustrated symposiums can be held in many hospitals or meeting halls in widely scattered cities at the same time.

The living record of an operation or of the history of a medical case, moreover, can be put on magnetic color tape for leisurely viewing and study in the future. In the hospital, a skilled supervisor at a central control station can literally "see" the entire institution without moving from his seat, dispatching nurses and doctors to points where they are needed.

Many of you are aware that the nation's first assembly of closed-circuit compatible color television for hospitals and research laboratories has been installed by the Radio Corporation of America at the Walter Reed Army Medical Center in Washington, D. C. It interconnects the Armed Forces Institute of Pathology, the Army Institute of Research, and the Walter Reed Army Hospital. The benefits in efficiency, coordination, saving of time, saving of manpower, and other respects, I am told, are already impressive.

The same instrumentality, closed-circuit TV, is finding more and more employment in education. Groups and individuals all over the country can hear and view illustrated lectures simultaneously. This makes possible not only specialized instruction for medical and nursing students but more convenient and more economical postgraduate courses for interns and refresher courses for practicing physicians.

It means that vital information and skills in one community have become readily available to the rest of the country. It means that the genius of an outstanding teacher or specialist, hitherto confined to one university or hospital, can be made accessible to interested men and women anywhere. In a period when significant new medical knowledge and techniques are constantly being unfolded, this electronic ability to disseminate them widely and rapidly should prove of inestimable value.

Electronic Computers for Biological Studies

Equally important is the ever-expanding contribution of electronic computers to biological, medical, and related sciences. Every physician, every researcher, every hospital struggles with the burden of rapidly accumulating data requiring classification, analysis, storage for instant availability for reference or study. An ever-larger share of that burden is being assumed by modern electronic data-processing equipment, with tremendous economies in time and gains in precision. Electronic performance provides almost instantaneously the kind of statistical and probability findings which would, by conventional methods, have required days or weeks of tedious work.

This element of time-saving is more important than might appear at first glance. In all areas of research, what is called the lead-time gap—the interval between the discovery of a basic principle and its practical application—is unduly long. But in biological work the gap is particularly protracted, owing to the extreme complexity of biological systems and the great caution essential when human health and life are at stake.

This is where the electronic worker comes increasingly to the assistance of the biologist. To begin with, speedy communication makes available

to each experimenter the new knowledge of others in the field. Often needless duplication of effort is thus avoided and the pieces of an emerging puzzle are more swiftly fitted together. Beyond that, automatic analysis of masses of data sharply telescopes the time ingredient.

Consider, for example, the complexity of the action of the endocrine glands. We know broadly that certain mechanisms control hormonal secretions, the effects of these hormones, and their elaborate interactions. Definitive conclusions, however, have been hampered by lack of sufficient data, speedily and accurately analyzed and reduced to dependable statistical forms. The enlistment of electronic "brains" in the enterprise obviously should shorten and sharpen the processes of inquiry.

Now that we have learned how to split the atom and how to reconstitute new atoms from old ones, or from energy itself, perhaps it is not too much to hope that the combined efforts, knowledge, and skills of biologists and electronic scientists may lead to a deeper understanding of the human cell and to the discovery of means for modifying its structure and its functions. Once this is achieved, we may find the answer to such dread diseases as cancer.

Electronics and Biology—Sister Sciences

Viewed from this broad perspective, we can say that the youngest of sciences, electronics, and one of the oldest, biology, are converging sciences. The very complexity of man's structure and its electrochemical aspects points up the natural relationship between them.

Electronic devices have the extreme sensitivity the biologist needs when delicate structures or tenuous phenomena must be examined. They can probe deeply and delicately and provide high magnification of what the apparatus finds. Only electronics is able to deal with the ever-increasing volume of data of biological structure and function.

Of course, it is dangerous to push affinities and analogies to excess. We must never forget that the stuff of life transcends, in its complexity, the most ambitious inventions man can imagine, let alone construct. Even the most elaborate man-made apparatus is primitive when matched against a living creature. The largest electronic computer, for example, may have one million storage elements, whereas the human brain has perhaps a hundred billion cells.

In any scientific endeavor, humility rather than pride is nourished by progress. For we realize that the more we learn, the more remains to be learned. Even in its most spectacular achievements, science can imitate but can never surpass the marvels of the Divine order.

It was by watching the effortless soaring of birds in the skies that Leonardo da Vinci and experimenters after him were emboldened to attack the problem of heavier-than-air flight. Radar is but a partial replica of the mechanisms whereby a bat finds its way in darkness past obstacles. The electronic submarine navigational equipment called sonar does not approach in perfection the means by which fish guide themselves under water. Man, in the final analysis, invents nothing that is more than a pale shadow of nature, from which he draws his inspiration and his material.

Yet the new science of cybernetics has shown that somewhat similar controls, feedbacks, and methods of operation prevail in man's electronic handiwork and in man himself. It is too early to judge the ultimate meaning and utility of these affinities. It is premature, too, to speculate in any detail on what the skilled electronic designer may accomplish in the future. Suffice for our time that electronics and biology are now treading a common path of inquiry, thrilling in its possibilities.

I have the utmost enthusiasm concerning the prospects of biology and electronics in their collaboration for the service of mankind. I am convinced that their relationship, already so close, is destined to become closer and more fruitful with every passing year.

The time may well come when science shall have fully uncovered the nature and functioning of both the energy-packed atom and its combinations on the one hand, the living cell and its aggregations on the other. At that point knowledge of the nature of life itself—the ultimate unity under the appearances of infinite diversity—may be revealed to us.

We in the electronics field believe that our labors will expand and enrich yours. At the same time we know that we shall continue to learn much that is helpful to electronics from your victories in the biological realms.

This rough sketch of some of the roads at which electronics and biology meet, is necessarily incomplete. However, I hope it may serve further to stimulate the curiosity and intensify the interest of scientists, researchers, and practitioners in both these fields. Their combined efforts, I feel certain, will lead to new discoveries and devices that will advance the health and welfare of all mankind.

30 Rockefeller Plaza (20).

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

The Concept of Early Diagnosis in Strokes. R. G. Siekert and C. H. Millikan. A.M.A. Arch. Int. Med. **101**:872-880 (May) 1958 [Chicago].

Focal cerebral ischemia or infarction (commonly referred to as thrombosis) accounts for some 80% of all strokes. In the absence of specific measures for the prevention of cerebral atherosclerosis, attention need be drawn to means that can be utilized to anticipate and thereby possibly prevent the occurrence of selected varieties of strokes. Three syndromes are delineated: the syndrome of intermittent insufficiency of the vertebral-basilar arterial system; the syndrome of thrombosis within the basilar arterial system; and the syndrome of intermittent insufficiency of the internal carotid arterial system. Illustrating case histories are presented with each of these 3 syndromes. The syndrome of intermittent insufficiency of the vertebral-basilar arterial system consists of sharply episodic attacks of visual dimness, weakness of the limbs (monoparesis, hemiparesis, quadriparesis), dysarthria, dysphagia, diplopia, confusion, and vertigo in various combinations. Between attacks the patient is well. During an attack, neurological abnormalities are present. A single episode may suggest the diagnosis if it includes most or all of these symptoms. Usually, however, a single episode is a fragment of the whole, and one can only suspect the diagnosis. It is when a group of these episodes occurs over weeks or months with the inclusion of most of the above-mentioned symptoms that one can be more certain of the diagnosis. Careful study need be made to determine that intermittent vascular insufficiency is the fundamental factor involved, rather than some other cause, such as an expanding intracranial mass or epilepsy.

The neurological signs noted in the second syndrome when thrombosis with the basilar artery is in the process of occurring or has actually occurred include the following: weakness of the limbs, often with extensor spasms; pseudobulbar or bulbar weakness in the form of dysarthria and dysphagia with a weakened pharynx and palate and slowness and decreased protrusion of the tongue; ocular abnormalities, particularly in the pupils, where inequality, miosis, and nonreaction may be seen, or in the extraocular muscles, which are weakened in various combinations; homonymous hemianopsia, which may be bilateral; and facial weakness, either "central" or "peripheral" in type. The last, with contralateral hemiparesis, usually indicates involvement of the brain stem. Hyperpyrexia is common.

The syndrome of intermittent insufficiency of the internal carotid arterial system consists of attacks of unilateral impairment of motor or sensory function or both. With involvement of the artery to the dominant hemisphere, aphasic disorders may be seen. Decrease in vision or blindness in only 1 eye (amaurosis fugax), and that on the side of the involved artery, will be seen in some instances. While the degree of involvement will vary, the complexity is not as great as in vertebral-basilar insufficiency. Here, too, a single attack may in no way be diagnostic, but a group of attacks may permit one to make the diagnosis. With early recognition of these types of cerebrovascular disease, treatment may be instituted prior to the possible occurrence of extensive cerebral infarction. Treatment with anticoagulant drugs may prevent the continuation of these ischemic attacks and, therefore, also the possible occurrence of a catastrophic infarction.

The Fate of the Patients with Persistent Cavitation and Noninfectious Sputum ("Open-Negative") After Discharge from the Hospital. R. F. Corpe and F. A. Blalock. Am. Rev. Tuberc. **77**:764-777 (May) 1958 [New York].

This report presents the preliminary experience of the authors with so-called "open healing" of tuberculosis cavities and with patients who have acquired a noninfectious status despite persistent cavitation under drug therapy. Between July 1, 1953, and Dec. 31, 1956, 159 patients with cavitary disease, sputum negative for tubercle bacilli, and pulmonary lesions stable on roentgenography were discharged from Battey State Hospital, Rome, Ga., and continued on drug therapy. On the basis of follow-up studies on these patients, the authors reached the following conclusions: It is safe to dis-

The place of publication of the periodicals appears in brackets preceding each abstract.

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charge patients with the "open-negative" syndrome to their home environment without creating a public health problem. The mortality rate in this group of patients was 3.8%, but these deaths occurred in patients who had not had bacteriological or roentgenologic relapse. They were not treatment failures. The reactivation rate was 8.8%. There were no additional reported bouts of suppuration or hemorrhage. There has been no discernible difference, up to the present time, in the reactivation rate between the Negro and the white race. The male sex has not fared as well as the female sex, 13 of the 14 reactivations occurring in men.

Only 2% of the patients were confined to their homes because of their physical disabilities. If such people can be adequately cared for in a home situation, they are much happier, and it is cheaper to maintain them on drugs outside the hospital than as inpatients. A considerable number of these people, even with cavitary disease, if given the opportunity, with public health clearance as to noninfectiousness, can become self-supporting and again take their place in society. Forty-five per cent of the patients had unlimited activity, and more than 25% were found to be working full time. The authors feel that these observations somewhat counterbalance their earlier belief that these cavities should be removed surgically or collapsed by thoracoplasty prior to the time when the patients could hope to return to their families and earn a living. Long-term follow-up observations on patients in this category are of extreme importance, since there are many unanswered questions, such as: How long should a patient with the "open-negative" syndrome be continued on drug therapy? This must be individualized, but a considerable number of these people should be continued on drug therapy indefinitely. On the other hand, among the group of 38 patients whose drug therapy had been stopped, there have been no reactivations to date.

Heart Failure of the Hunchback. T. Hanley, M. M. Plattis, M. Clifton and T. L. Morris. Quart. J. Med. **27**:155-171 (April) 1958 [Oxford, England].

This paper deals with 24 persons with severe hunchback. Ten of these patients had severe kyphoscoliosis and heart failure. The clinical features, arterial blood-gas values, and pulmonary function of these 10 patients were compared with those obtained in the 14 persons who had severe spinal curvature but had not suffered from heart failure. It was found that severe kyphoscoliosis may reduce the total lung capacity and the vital capacity to as little as one-quarter of normal. The diminutive lungs are, however, ventilated with an efficiency only a little less than normal, and emphysema is usually slight. The diagnosis of kyphoscoliotic heart disease did not present great difficulty. In kyphoscoliotic heart failure peripheral vascular signs were predominant, and the clinical picture closely resembled that of anoxic cor pulmonale due to emphysema.

Reduced arterial oxygen saturation and retention of carbon dioxide were found in 8 of the 9 patients with true kyphoscoliotic heart disease, but these changes were present in only 2 of the 14 patients without heart failure. It was not possible to make such a clear distinction, simply by measuring either the volumes of the various compartments of the lungs or the efficiency of ventilation, between those with and those without a history of heart failure. Cardiac catheterization was done in 3 patients; it showed a moderate rise of the pulmonary artery blood pressure in 2 anoxic patients who had recovered from heart failure and a small rise in 1 patient who had not had heart failure.

Clinical and Microbiological Aspects of Salmonellosis. G. M. Eisenberg, L. Brodsky, W. Weiss and H. F. Flippin. Am. J. M. Sc. **235**:497-509 (May) 1958 [Philadelphia].

In a previous report on 95 patients with salmonellosis seen during 1947-1952 at the Philadelphia General Hospital, it was pointed out that diagnosis on clinical grounds alone was frequently hazardous in view of the protean nature of the clinical manifestations. The practical importance of employing diagnostic antigens capable of demonstrating serum antibodies resulting from infections induced by Salmonella organisms, other than the classical typhoid-paratyphoid strains, was illustrated. Information on an additional 75 cases of bacteriologically proved Salmonella infections during the period from January, 1953, to June, 1957, was obtained subsequently from a review of records at the same institution, and it is these data which form the subject matter of the present report. The current study includes results of antibiotic susceptibility tests on cultures of the various Salmonella serotypes. Of the 75 patients comprising the study group, 40 were adults and 35 were infants and children.

Fever and diarrhea were encountered most frequently in both pediatric and adult patients, diarrhea being more common in the former. The proportion of patients with fever and the occurrence of vomiting was about the same in both groups. The over-all mortality rate was 20%; however, if the estimation of mortality is based only on those cases in which death was unquestionably attributable to the salmonellosis, the fatality rate is reduced to 5.3%. Fatalities occurred among infants and older debilitated individuals. In contrast to the experience in the 1947-1952 series, in which most of the deaths were associated with infection by Salmonella organisms of serogroup C, mortality in the present study was associated with strains be-

longing to serogroup B. Evidence is presented to support the view that any of the several clinical syndromes may be produced by the same or different Salmonella serotypes. The length of time that these organisms continue to be shed in the stools after apparent clinical cure of the patient is variable. Where such information could be obtained, this interval has ranged from 10 to 604 days, with an average of 127 days. In vitro antibiotic susceptibility testing of the 62 salmonellas isolated from patients revealed them to be uniformly sensitive to chloramphenicol. About one-half of the strains were susceptible to the tetracyclines, streptomycin being quite ineffective. No relationship between serotype and antibiotic susceptibility could be detected. Despite the in vitro superiority of chloramphenicol, its clinical use, either alone or concomitantly with other agents, exerted little, if any, influence upon the fatality rate.

The Treatment of Eosinophilic Lung (Tropical Eosinophilia) with Diethylcarbamazine. T. J. Danaraj. Quart. J. Med. 27:243-263 (April) 1958 [Oxford, England].

Earlier the author had demonstrated the efficacy of organic arsenicals in eosinophilic lung. The use of organic arsenicals, however, is associated with definite risks, so that a search was made for some form of treatment as effective but not toxic. Groups of patients were treated with various drugs—sulfathiazole, bismuth, penicillin, Achromycin, cortisone, piperazine citrate, and diethylcarbamazine—but only diethylcarbamazine was found to be of value. As diethylcarbamazine is known to be effective in the treatment of filariasis, it was important to exclude this disease. There was no evidence suggestive of past or present filarial infection in any of the 110 patients analyzed in this report. The duration of illness when they were first seen was variable, the shortest period being 1 week, and the longest 4 years; in the majority of the patients (97) it was under 6 months. The initial complaint was cough, which was most frequent and severe at night, occurring in paroxysms of a few minutes and productive of slight mucoid or mucopurulent sputum, which was sometimes streaked with blood; sleep was badly disturbed. A feeling of suffocation and breathlessness was usually present after each bout of coughing, and at times was severe enough to resembled bronchial asthma. The severity of symptoms was considered to be slight (cough only) in 9 patients, moderately severe (cough with breathlessness) in 75, severe (bronchial spasm) in 25, and very severe (status asthmaticus) in 1 patient. Occasional bouts of low fever, lasting for a few days, were noted in 24 cases. No history of allergy was obtainable, except in 1 patient, who suffered from attacks of urticaria. A family history of bronchial asthma was given by 6 patients. Abnormal physical signs, which were confined to the chest, were present in 88 patients and consisted of coarse crepitations and rhonchi heard over the bases of the lungs, together with bronchial spasm in 26 patients. In nearly all the patients radiologic examination of the chest revealed increased striations, with varying degrees of mottling.

The dosage of diethylcarbamazine given initially to 46 patients was that generally recommended in the treatment of ascariasis: 4 mg. per kilogram of body weight given 3 times daily for 4 days. Later, 2 larger dosages were tried: 6 mg. and 10 mg. per kilogram of body weight given thrice daily for 5 days to groups of 57 and 7 patients respectively. The average total adult dose for each of the 3 dosage schedules was 3,200 mg., 6,000 mg., and 10,000 mg. respectively. The drug was given after meals in the form of 50-mg. tablets, the sirup being used for children. Except for 11 patients who exhibited severe bronchial spasm and were treated with antispasmodics as well, the patients were given only diethylcarbamazine. The drug proved to be safe and effective in the 110 patients with eosinophilic lung. It had no effect on patients suffering from other diseases with eosinophilia. The results obtained compared favorably with those obtained with organic arsenicals. Diethylcarbamazine should replace the organic arsenicals, because the latter sometimes result in encephalopathy and death in a disease which, although incapacitating, has no mortality in itself.

Hypogammaglobulinaemia and Tuberculosis: Implications of Their Association, and Other Observations. R. Parkes. Brit. M. J. 1:973-976 (April 26) 1958 [London].

The author reports on a 22-year-old unmarried woman who from the age of 4 years had recurrent colds and from the age of 5 years had typical grand mal epilepsy. Pulmonary tuberculosis occurred at the age of 19 years, for which the patient was treated with streptomycin and isoniazid. The tuberculous upper-lobe consolidation in the right lung, which was present on admission to hospital, resolved over a period of 6 months. Bronchograms obtained 2 years after the institution of the antimicrobial therapy showed moderately severe "saccular" bronchiectasis of the anterior and apical segment of the upper lobe of the right lung. Otherwise the bronchial tree appeared entirely normal. Two years after tuberculosis was detected, acquired hypogammaglobulinemia was diagnosed on the basis of the history of continued bacterial infection, gamma-globulin deficiency on paper electrophoresis, zinc sulfate turbidity test, fractional precipitation, and absence of isohemagglutinins. Gamma-globulin replacement therapy was instituted with 0.5 Gm. per kilogram of body weight in 1 week as a loading dose, followed by 0.025 Gm.

per kilogram of body weight per week for 4 months. The patient was given 0.5 Gm. of gamma-globulin per kilogram of body weight per week for an additional 4-month period. She also was given methoin and phenobarbital in small daily doses as anticonvulsants. After 6 months' replacement of gamma-globulin, its serum level had increased more than threefold. Fewer grand mal seizures occurred, and petit mal attacks were rarely observed. Electroencephalograms were impressively better. Despite this striking improvement, there was no apparent connection between hypogammaglobulinemia and epilepsy. The patient was animated and cheerful, when previously she had been dull and lethargic. Respiratory infections and frequent inexplicable low-grade fever no longer occurred.

The patient's history suggested the presence of hypogammaglobulinemia 5 years at least before pulmonary tuberculosis developed, and tuberculosis was known to have been present for 2 years before gamma-globulin therapy was instituted. The association of hypogammaglobulinemia and tuberculosis is probably coincidental, and they bear no cause-and-effect relationship to one another. The natural course of tuberculous disease appears to be unaffected by hypogammaglobulinemia. Both delayed hypersensitivity and serum antibody response to tuberculosis appear to function normally in patients with hypogammaglobulinemia, so that in normal persons the 2 phenomena may be independent of gamma-globulin and may be to a large extent related to a cell mechanism (leukocytes and other body cells), although the possibility of an unidentified serum protein fraction sharing such immunological powers is not excluded.

Hypertension and Diabetes Mellitus. P. Freedman, R. Moulton and A. G. Spencer. Quart. J. Med. 27:293-305 (April) 1948 [Oxford, England].

The blood pressure was measured in 1,100 patients attending a diabetic clinic, and the data were analyzed in terms of the incidence of hypertension in each age and sex group. Hypertension was common in both sexes, and the incidence steadily increased with age to a maximum of 92% of the female and 81% of the male diabetics at 70 to 79 years. A strong clinical impression was gained that hypertension was more common in diabetics than in a general hospital population. Statistical analysis, however, clearly showed that this difference is largely a false impression due to the abnormal age and sex distribution of the diabetic population. From 10 to 69 years of age, in both sexes, there was no significant difference in the incidence of hypertension in diabetics as compared with a nondiabetic population. It was only at 70 to 79 years that high blood pressure was distinctly more common in diabetics.

Severe hypertension (diastolic pressure over 125 mm. Hg) is rare in diabetes, the incidence being 0.5% in the male and 1.4% in the female subjects, which is less than in a general hospital population. Advanced hypertensive retinopathy, excluding diabetic retinopathies, was not seen in any of the diabetic subjects, except in those with pheochromocytoma. Data are given on the apparent incidence of hypertension due to various renal and endocrine disorders in diabetes. Diabetic nephropathies were diagnosed in 27.5% of the patients whose diastolic blood pressure was over 100 mm. Hg. The arm circumference was measured in all the hypertensive diabetic subjects and was found to be an important factor in determining the level of the blood pressure in 26.5% of these patients.

SURGERY

Acute and Chronic Thrombosis of the Mesenteric Arteries Associated with Malabsorption: A Report of Two Cases Successfully Treated by Thromboendarterectomy. R. S. Shaw and E. P. Maynard. New England J. Med. 258:874-878 (May 1) 1958 [Boston].

The authors report on 2 men, aged 54 and 58 years, respectively, with occlusion of the superior mesenteric artery resulting in intestinal ischemia associated with malabsorption. The first patient had been admitted to hospital because of progressive bilateral intermittent claudication. Aortography showed a narrowed aortic bifurcation and complete occlusion of the right external iliac artery. The patient was operated on, and an aortic homograft was sutured end-to-side to the abdominal aorta, the right limb of the graft being anastomosed end-to-side to the common femoral artery and the left to the popliteal artery. On the third postoperative day the patient had abdominal cramps and passed a liquid stool containing occult blood. The abdomen remained nontender until the 16th postoperative day, when suddenly severe generalized abdominal pain occurred and peristalsis disappeared. At reexploration 9 hours later the entire small and large intestines from the ligament of Treitz through the midsigmoid appeared pale and cyanotic. There were no pulsations in the celiac axis, in any of its 3 major branches, or in the superior mesenteric artery and its branches. A pancreatic necrosis was observed, which appeared to be of at least 1 week's duration. The superior mesenteric artery was opened through a longitudinal incision and was found to be occluded by a brownish thrombus and atheroma in its proximal 2 cm. A proximal thromboendarterectomy was performed through this arteriotomy with resultant excellent flow from the aorta. An amazing recovery of the small intestine resulted, while the large intestine

remained cyanotic. A loop transverse colostomy was performed, so that the circulation of the colon could be observed in the postoperative period. Localized signs of peritonitis developed on the second day, and exploration was again carried out. The colon remaining within the abdomen was obviously viable, although there were 2 or 3 small necrotic areas in the wall of the defunctioned transverse colon. These were surgically patched with tabs of fat. The appendix was necrotic, and appendectomy was performed. Colostomy diarrhea and abundant drainage from the wounds, with the occasional casting out of a piece of pancreatic slough, continued for several weeks. The stools were found to contain increased amounts of fat. One month after the operation studies of intestinal absorption were performed, which showed a considerable defect in the absorption of fat, sugars, and vitamin B_{12}, with improvement during the 4-week period of observation. The patient was discharged 2 months after the thromboendarterectomy; he gained weight, was free from gastrointestinal symptoms on an unrestricted diet, and resumed full-time work.

These observations suggested that atherosclerotic occlusive disease in the arteries of the abdominal viscera may behave as it does in the brain, heart, and extremities, progressing more rapidly than collateral circulatory development and producing a picture of malabsorption, intermittent abdominal gain, and weight loss terminating in acute intestinal infarction. This was the sequence of events which occurred in the second patient in whom absorption studies were performed before and after the surgical correction of chronic intestinal ischemia and in whom the diagnosis was established preoperatively by aortography. Although major arterial branches to the abdominal viscera other than the superior mesenteric artery were involved with occlusive disease, restoration of continuity in the superior mesenteric artery alone was sufficient to provide symptomatic relief of ischemia. Since the absorptive functions of the intestine may be assumed to be dependent on its blood supply, it is not surprising that impairment of this supply should be accompanied by malabsorption. The diagnosis should be considered in certain patients with unexplained malabsorptive states, and thromboendarterectomy may represent an effective therapy in these patients, as well as in those in whom mesenteric vascular thrombosis results in intestinal infarction.

Lung Resection in Tuberculosis. I. S. Kolesnikov. Vestnik. khir. 8:3-10 (March) 1957 (In Russian) [Leningrad].

Kolesnikov reports on 1,000 pulmonary resections performed for pulmonary tuberculosis in Leningrad during the past 5 years. The indications for elective resections were strict. The majority of the patients operated on had far advanced fibrocavernous tuberculosis. The sputums of all the patients were positive for tubercle bacilli. The patients selected for resection were those that showed no improvement from other methods, including collapse therapy. Pneumonectomy was performed on 23.3%, bilateral lobectomy on 4.6%, lobectomy on 30.6%, segmental resection on 28%, and various other types of resections on 13.5%. Endotracheal potentiated ether-oxygen anesthesia was used in 950 cases. Fifty patients were operated on under local anesthesia. The author stresses the desirability of resecting as little as possible of the lung. He does not rule out the employment of pulmonary collapse and of cavernostomy, each of these operations having its own indications. A closer contact between surgeons and internists should bring about earlier transference of patients to the surgeon and in that way should diminish the number of mutilating operations, such as pneumonectomy and bilateral lobectomy, and at the same time should increase the number of segmental resections.

Segmental Occlusion of the Femoral Artery and Femoral and Popliteal Aneurysms: Surgical Aspects. D. A. Felder and T. O. Murphy. Minnesota Med. 41:322-326 (May) 1958 [St. Paul].

The authors used autogenous and homogenous veins, crimped braided nylon tubes, and compressed Ivalon sponge tubes for iliac-femoral arterial shunts or replacements in 24 patients and for femoral-popliteal arterial shunts or replacements in 73 patients. In the group of 24 patients, successful vein grafts existed more than 2 years in 7 of the 8 patients in whom they were used; the nylon tubes used at this level in 5 patients remained open for from 3 to 12 months. Of the compressed Ivalon prostheses used in the remaining 11 patients, 6 failed; the successful Ivalon sponge grafts were all patent over 14 months. In the group of 73 patients, vein grafts were used in 37, nylon tubes in 32, and Ivalon sponge prostheses in 4. Successful vein grafts existed 5 to 24 months after surgical treatment in 29 of the 37 patients. Sixteen of 32 nylon tube shunts were still open 3 to 12 months after the operation. The compressed Ivalon prostheses failed in all 4 patients in whom they were used. Thus, the most satisfactory results in patients with long segmental occlusions in the iliac-femoral and femoral-popliteal areas were obtained with the use of autogenous saphenous veins and braided nylon tubes, both as shunts and as replacements.

Of 20 patients with popliteal aneurysms, 11 underwent lumbar sympathectomy with subsequent resection of the aneurysm in 3, 1 had a simple resection of the aneurysm, and in 8 primary resection with autogenous vein grafting was attempted after sympathectomy. Sympathectomy followed by im-

mediate resection appeared to be the most satisfactory method of treatment for the symptomatic or asymptomatic popliteal aneurysm. In 4 of the 8 patients in whom attempts at replacement with autogenous vein grafts were made, encouraging results were obtained in that these patients have functionally good extremities without claudication.

Short segment thromboendarterectomies were performed in 5 patients with acute arterial occlusions. Two of these were due to embolism and 2 to thrombosis. One of the 5 patients died within 24 hours after the operation, and autopsy revealed multiple emboli in the renal, splenic, and cerebral vessels. Another patient required a saphenous vein graft of the common femoral artery, since the remaining vessel after endarterectomy was too friable to hold sutures. This patient is well, with good peripheral pulses, 30 months after the operation. The remaining 3 patients had patent vessels on follow-up examination 3 months to 1 year after the operation. For short segments, and particularly in cases of acute occlusion, either by embolism or spontaneous thrombosis in severely sclerotic femoral arteries, endarterectomy is definitely necessary for a successful result.

Lung Resection in Tuberculosis. A. M. Dyhno. Vestnik. khir. **8**:10-16 (March) 1958 (In Russian) [Leningrad].

The author reports on 127 patients with fibrocavernous tuberculosis who were operated on. There were 5 pneumonectomies, 72 lobectomies, and 50 segmental resections. The onset of the disease dated from 1½ to 14 years. All the patients were treated preoperatively with antibiotics, artificial pneumothorax, and sanatorium rest. There were 8.8% postoperative deaths, the cause being shock in 4 patients, hemorrhage in 2, and empyema in 2. The postoperative course was complicated in 4.9% by a bronchial fistula and in 12.7% by empyema.

Surgical Methods of Treatment of Tuberculosis of Children and Adolescents. M. L. Shulutko. Vestnik khir. **80**:16-23 (March) 1958 (In Russian) [Leningrad].

Cavernous types of tuberculosis of children and adolescents give unfavorable prognosis when treated conservatively. The introduction of streptomycin and of other chemical therapeutic substances has not solved the problem. Surgical methods are beginning to play an important role in the complex treatment of children and adolescents with cavernous pulmonary tuberculosis. An analysis of 131 patients operated on gave a postoperative mortality of 3%; there was empyema in 2.3% and bronchial fistula in 3.8%. Follow-up revealed deaths from tuberculous process on the operative side in 2 patients. The remaining 120 patients (91.6%) are practically well and free from tubercle bacilli. Attention is called to the fact that the mediastinum in children and adolescents has considerable mobility. The author therefore advocates introduction of a pneumothorax 3 to 5 days before the operation. This results in gradual replacement of the mediastinum and in giving the general organism an opportunity to adapt itself to new conditions. Pulmonary resection is indicated for the following conditions: (1) in the presence of multiple cavities of the lung; (2) in patients with marked fibrosis surrounding a pulmonary cavity; (3) in the presence of tuberculous lesions and bronchiectasis; (4) in patients with bronchial stenosis; (5) in the presence of diffuse lobar infiltration after preliminary but ineffective antibacterial therapy; (6) in cases of caseation of the lung; (7) after prolonged but ineffective pneumothorax; and (8) after ineffective thoracoplasty, extrapleural pneumothorax, and oleothorax; employment in these patients of thoracoplastic procedures and of extrapleural pneumothorax is seldom successful. One of the peculiarities of the course of tuberculosis in children and adolescents is bilateral involvement. Of the 441 children treated in the author's clinic, 45 to 50% presented bilateral involvement. They were treated by artificial pneumothorax of one side and operative resection of the other side. The important problem in the treatment of bilateral tuberculosis is the maximal sparing of healthy tissue. This is best accomplished by a sparing bilateral resection.

Aneurysms of the Thoracic Aorta. F. H. Ellis Jr. Minnesota Med. **41**:335-338 (May) 1958 [St. Paul].

The author reports on 24 patients, between the ages of 5 and 73 years, with aneurysms of the thoracic aorta which were arteriosclerotic in 10, syphilitic in 5, traumatic in 4, congenital in 2, mycotic in 2, and dissecting in 1. Resection of the lesion was done with the aid of hypothermia in 18 of the 24 patients. The main cause of inoperability was the location of the aneurysm in either the ascending aorta or its proximal arch. Grafts were used in 17 of the 18 patients on whom resection was done. Homografts were used in 14 patients, an Ivalon sponge graft in 2, and a crimped nylon tube in 1. Hypothermia was used as a means of avoiding ischemia of the spinal cord during cross clamping of the aorta. By reduction of the arterial oxygen requirement of the central nervous system, a safe period of aortic occlusion up to 1 hour is permitted. Six patients died in the first week after the operation. Hemorrhage, complications of hypothermia, or both accounted for most of the deaths. In only 1 patient were neurological signs and symptoms recognized in the postoperative period. Three other

patients died later, and death resulted from hemorrhage in all. Aneurysm of the thoracic aorta is a serious threat to health and life, and its surgical removal should be considered seriously despite the high mortality rate.

Clinical Importance of Traumatic Fat Embolism. H. Kühne and K. H. Kremser. Beitr. klin. Chir. **195**:385-394 (No. 4) 1957 (In German) [Munich, Germany].

Autopsies in 643 fatal traffic accidents during the years from 1954 to 1956 revealed fat embolism of the lungs in 95%; it was massive in 59%, and the systemic circulation was involved in 23%. Since autopsy findings indicate the terminal status and do not permit deductions regarding clinical conditions, the authors investigated the presence of air embolism in patients with comminuted and open fractures, in those with traumatic décollement, and in those subjected to fracture nailing. One hundred fifteen of a total of 2,956 patients with such injuries died, and whereas fat embolism was found in all of those who died, the clinical diagnosis of fat embolism was made during life in only 7 of the patients whose histories are presented. Five of these 7 patients had sustained severe traffic accidents, and the other 2 had fallen from great heights. They had sustained multiple fractures. In 1 case extensive décollement was associated with a pelvic fracture and fractures of the leg and femur.

All the patients were conscious on admission to hospital, but they were in shock. After measures were taken to counteract the shock, 6 patients responded with rapid recovery, but 5 died after intervals of from 1 to 4 days with signs of respiratory insufficiency. Case 7 is of particular interest, because pulmonary as well as cerebral symptoms indicated extensive fat embolization, but the patient apparently was able to cope with these emboli, because at the time of his discharge he was free from all neurological disturbances. The severe shock existing in all patients decided the therapeutic measures. Only 1 of the patients (case 7) could be given specific therapy in the form of dehydrocholic acid (Decholin) and eupaverin, whereas in the others death occurred so rapidly that there was no time for such treatment. In the further discussion of fat embolism, the authors consider not only the cases reported but also literature reports.

Cavernous Hemangiomas, "Cavernomas" of Liver. F. Niemann and W. Penitschka. Beitr. klin. Chir. **195**:257-277 (No. 3) 1957 (In German) [Munich, Germany].

The authors report on a 44-year-old woman with cavernoma of the liver who was operated on at the surgical clinic of the University in Bonn, Germany. She had severe epigastric pain during the 7 months before surgical intervention and had lost a considerable amount of weight. Roentgenologic examination of the gastrointestinal tract, heart, lungs, and urogenital tract did not reveal any abnormality. Laparotomy revealed a partly nodulated and partly smooth tumor, the size of the head of a child, which partly adhered to the parietal peritoneum; it occupied the entire left epigastrium up to the umbilicus and was connected with the liver. There was a distinct border line between the diseased and the normal tissue of the liver. The left enlarged lobe of the liver which was entirely occupied by the tumor was resected. Microscopic examination of the surgical specimen revealed a typical cavernoma. The course of healing was delayed for 8 weeks by a seropurulent secretion which originated in a cavity below the left costal arch at the border of bone and cartilage, suggesting a cartilaginous necrosis. The patient was discharged in excellent general condition 10 weeks after the operation. She had gained 5 kg. (11 lb.).

One hundred two additional cases of surgically removed cavernoma of the liver were collected from the literature. Thirteen (12%) of these tumors had perforated. The primary mortality rate among patients operated on was 11%. The best operative results were obtained with the radical extirpation of the tumor, whether the tumor had ruptured or not. Despite the fact that hemostasis was frequently difficult, only 2.5% of the patients undergoing resection died, as compared with 90% of those in whom only tamponade was used for a perforating cavernoma. In 7 patients the size of the tumor decreased as a result of roentgenotherapy, injections promoting sclerosis, or galvanocautery. Late results of surgical treatment were reported in 16 of the 102 patients with cavernoma of the liver who were followed for 2 to 10 years; all of them were in good health and completely free of complaints. True recurrences were not reported.

A Further Description of the Pathologic Physiology of Congenital Megacolon and the Results of Surgical Treatment. R. B. Hiatt. Pediatrics **21**:825-831 (May) 1958 [Springfield, Ill.].

The author reports follow-up results of 63 patients who were operated on for congenital megacolon at the Columbia-Presbyterian Medical Center, New York, between 1947 and 1955. There were 5 deaths, 3 of which occurred in infants whose age at the time of the operation was less than 12 months and were due to severe enterocolitis occurring from 3 months to 1 year after the operation. The 4th early postoperative death occurred also in an infant less than 12 months of age, and was due to acute aspiration in the nursery. The 5th death occurred in a child whose age at the time of operation was 18 months and who died at 3 years of age of acute

membranous colitis. The 58 surviving patients had undergone a "pull-through" procedure, consisting of a surgical intussusception of the entire rectum and the lower two-thirds of the sigmoid through the anus, with replacement by more proximal colon and with an end-to-end anastomosis of the anus and sigmoid in one stage. Twenty-nine (50%) of these patients were completely continent immediately after the operation or within 1 year after the operation; 20 patients (34%) became completely continent within 2 to 5 years after the operation; and in 9 patients (16%) fecal staining or actual incontinence is still a persistent problem after many years. Careful observation of these 9 patients with imperfect anal control revealed that enterocolitis and psychological maladjustment are the 2 prominent factors which contribute to this difficulty.

In congenital megacolon one is dealing with a slowly progressive disease as a result of gradual development of hypertrophy in the proximal portion of the aganglionic segment of the colon; this hypertrophy in time increases the degree of obstruction, because its response to the constant physiological stimulus of feces occurs in the form of nonpropulsive spasm. This hypothesis explains why good initial results may be obtained from a segmental resection of the transitional segment, since, although only a part of the aganglionic segment is removed, the hypertrophied portion which is responsible for most of the obstructive element is removed. This initial good result, however, can only be temporary, since obstruction is bound to occur when hypertrophy develops again in the remaining achalasic segment. The replacement of the rectum and the lower sigmoid by proximal colon in patients with congenital megacolon has proved successful, as manifested by the long-term follow-up study.

NEUROLOGY & PSYCHIATRY

Barbiturate Narcomania as Problem in Medical Department with Resident Psychiatrist. E. Kåss, N. Retterstøl and T. B. Sirnes. Tidsskr. norske lægefor. **78**:341-345 (April 15) 1958 (In Norwegian) [Oslo].

Of 3,750 patients admitted to a medical department with a resident psychiatrist during a 2-year period, 63 were drug addicts. Sixty patients (40 men, 20 women) were addicted to barbiturates alone or combined with other narcotics, 44 of them being admitted because of acute intoxication. In more than half of the cases there was also chronic alcoholism. Fifteen patients had had long-term treatment with narcotics prescribed for illness. In the remaining patients the main cause of the addiction was attributed to personality deficiency. More than half of the patients were without work. Abundant amounts of vitamins B and C were given, often combined with insulin in small doses. Some patients were also given ataraxics (chlorpromazine, reserpine, meprobamate). In general, treatment of narcomania cannot be carried out well in a medical department, where the treatment of somatic symptoms is important. The patients were prepared by the psychiatrist to be motivated, if possible, for a long-term treatment in psychiatric institutions. There are no possibilities for narcomaniacs unwilling to be treated. The prognosis for permanent recovery in established narcomania is unfavorable. Greater weight should be put on prophylaxis.

Primary Amyloidosis with Special Reference to Involvement of the Nervous System. R. A. Chambers, W. E. Medd and H. Spencer. Quart. J. Med. **27**:207-226 (April) 1958 [Oxford, England].

Primary amyloidosis has been divided into cases in which there is 1 localized tumor and those in which the deposits are more generalized. The present paper describes 6 patients with the generalized forms, 3 of whom initially presented neurological problems. Various aspects of amyloidosis are discussed on the basis of these case histories and of literature reports. Approximately two-thirds of all cases occur in men, and the clinical form is partly related to age, neuropathy occurring relatively early and cardiac myopathy relatively late. The clinical picture varies but frequently shows the gradual onset without fever or toxemia, in adult life, of impaired function of the myocardium, kidneys, or peripheral nerves. The illness is progressive despite treatment and, if the heart or kidneys are involved, leads to death in a few years. The polyneuritis affects first and most severely the longest fibers. The symptoms are predominantly sensory, and usually the first symptom is pain, often lightning pains. The motor signs are those common to all types of chronic polyneuritis and may be of any severity. The characteristic sensory abnormality is diminished appreciation of temperature and pain. The ankle jerks, and later the other tendon reflexes, are lost, but they may be present when symptoms and cutaneous sensory signs are advanced. Additional clinical features include diarrhea, impotence, vitreous opacities, abnormal pupils, and thickened peripheral nerves.

That the diagnosis of amyloid neuropathy is difficult is demonstrated by the fact that chronic tonsillitis, dermatitis artefacta, hysteria, malingering, disseminated sclerosis, spinal tumor, tabes dorsalis, and leprosy were the diagnoses considered in the 3 patients who initially presented neurological problems. Amyloid polyneuritis may mimic tabes, but this diagnosis should be doubted if the motor symptoms are symmetrical and sphincter symptoms are absent. Examination of the blood and cerebrospinal fluid may be necessary. If leprosy

is likely, the social consequences make biopsy essential. Sensory radicular neuropathy is similar in many respects, including the family history and, sometimes, diarrhea and abnormal pupils, but wasting and weakness and enlarged peripheral nerves, all characteristic of amyloid polyneuropathy, are usually absent. Serum protein examination, the Congo red test, and biopsy are valuable diagnostic aids. Serum protein changes include diminished total protein, diminished albumin, and increased globulin values and the finding on electrophoresis of an abnormal protein, which may appear in the urine, in the region of the α_2–β globulin bands. In five of the 6 reported patients the total protein content and the albumin content were reduced or at the lower limit of normal. The Congo red test was performed for 3 of the patients. The result was positive in case 3, equivocal in case 1, and negative in case 6; the authors accepted 90% retention of dye in 1 hour as positive. The result probably depends on the amount of amyloid and its affinity for Congo red, and, although a negative result is of no significance, falsely positive results are rare. The authors conclude that amyloidosis, whether primary or secondary, is a single disease process, with variations in distribution determined by such factors as inheritance, age, and sepsis.

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Tuberous Sclerosis: Case Report. H. Mavor and G. A. Schumacher. J. Maine M. A. **49**:179-182 (May) 1958 [Brunswick].

The patient, a 37-year-old woman, was admitted to the neurology service of the DeGoesbriand Memorial Hospital in Burlington, Vt., on July 16, 1957, in status epilepticus. The history obtained on admission was meager. The patient apparently had had intermittent convulsive seizures for many years and had been treated with Dilantin capsules. This medication had been omitted for 2 days prior to admission. The onset of repetitive seizures occurred approximately 1 to 2 hours prior to admission. When first seen the patient was having successive focal and generalized convulsive seizures, consisting of tonic and clonic movements of the right upper and lower extremities, with occasional spread to the left, associated with apnea and cyanosis and followed by hyperpnea, coma, and widely dilated, unreactive pupils. The seizures were controlled with a total of 910 mg. of phenobarbital sodium given intravenously in divided doses over a 2-hour period. The presence of facial skin lesions resembling adenoma sebaceum, convulsions, and the deteriorated state implying mental retardation suggested a diagnosis of tuberous sclerosis. Hints of a familial incidence were obtained in that the patient's son suffered from "spells" and had never been able to attend school.

Tuberous sclerosis or epiloia, one of several recognized neurocutaneous syndromes, has as its outstanding manifestation the triad of convulsive seizures, mental deficiency, and skin lesions. Over 450 cases have been reported. In hospitals and colonies for the epileptic, the incidence among new admissions appears to be approximately 1 in 200. The disorder is congenital, and strong heredofamilial tendencies are present. Two major hypotheses are (1) that it is a disorder of prenatal development, i. e., of embryogenesis (blastomatous in origin), and (2) that it is actually a slowly progressive neoplastic process. One view has held that tuberous sclerosis and neurofibromatosis are similar, the former a central, the latter a peripheral neurospongioblastosis. Attention is usually called to the disease by the occurrence of convulsive seizures of both the major generalized type and the minor petit mal variety early in life. The coexistence with convulsions of mental deficiency and the characteristic butterfly distribution of small skin nodules, spreading from the nose over the cheeks and usually also involving chin and forehead, is sufficient to make the diagnosis. The brain in epiloia reveals grossly firm white nodules at the surface as well as deep in the cortex. Similar foci appear in the subcortical white matter. Tumor nodules may project into the ventricular cavities. Less often, nodules are also found in the basal ganglions, brain stem, and cerebellum. No specific therapy for the basic disease process is available. The usual anticonvulsants are employed to counteract seizure activity.

Is Cortisone Contraindicated in the Acute Phase of Polioencephalitis? R. De Mattia and F. Di Nola. Minerva med. **49**:1183-1187 (March 31) 1958 (In Italian) [Turin, Italy].

The authors believe that cortisone may be used effectively in the management of acute polioencephalitis when the functional blockage can be ascribed to the compressive action of edema and is thus at least partially reversible. Cortisone was given to 8 patients with polioencephalitis in 6 of whom the disease was accompanied by tetraplegia and by paralysis of the bladder muscles. Paralysis of respiratory and of swallowing muscles affected 2 patients, and paralysis of respiratory muscles alone affected 2. Cortisone was given parenterally to all patients, 3 of whom received it in a single dose in combination with hydrocortisone (25 mg.) by the intrathecal route. Total dosage of 450 to 900 mg. of cortisone was administered in decreasing divided daily dosages, from 200 mg. in the beginning to 100 mg. at the termination of treatment, for a period of 4 to 6 days. Six of 8 patients survived with fair chances of functional restoration. The results were good, although they may be only partially attributed to the effect of cortisone.

GYNECOLOGY & OBSTETRICS

Intra-Aortic Transfusion: Discussion of Technic and Report of Five Cases. H. L. Riva, J. L. Breen, R. P. Hatch and W. L. Pickhardt. Obst. & Gynec. 11:537-542 (May) 1958 [New York].

Five women, between the ages of 28 and 43 years, 2 with spontaneous rupture of the uterus associated with intrauterine pregnancy, 2 with ruptured ectopic pregnancy, and 1 with carcinoma of the uterine cervix, who underwent abdominal surgery, were in severe shock and responded inadequately to intravenous transfusion of blood. The abdominal aorta then was used as a site for transfusion. By displacing the intestinal tract onto the abdominal wall, rather than packing it, time was saved and better exposure of the aorta was obtained. The transfusion was carried out with an angulated aortic needle, which was inserted just above the bifurcation of the aorta. Exposure of the aorta was performed by vertically splitting the posterior peritoneum to allow better exposure for placing the needle and for repair of the vessel, if the need should arise, thus avoiding concealed retroperitoneal hemorrhage. Hemorrhage was controlled by clamping either the aorta or the common iliac arteries with vascular clamps.

Intra-aortic transfusion of about 500 cc. of blood brought about a rapid change in all the patients, with complete stabilization of blood pressure occurring within 5 to 20 minutes. In addition, the immediate perfusion of the coronary and cerebral vessels was of great importance at the time of intra-aortic transfusion. Intra-aortic transfusion was accomplished in each patient within several minutes. The danger of air emboli was avoided by discontinuing the transfusion just before its completion. In none of the patients was it necessary to repair the aorta after the transfusion, and no retroperitoneal hematomas were observed. There was no morbidity or mortality in this small group of patients. The aorta at the time of abdominal surgery is easily accessible for transfusion and has many advantages over other arterial vessels. Intra-aortic transfusion is simple and requires a minimum of equipment. It is of unquestionable value in many cases in which death from hemorrhage seemes inevitable.

Mumps Mastitis in the Nursing Female, with a Case Report. R. J. Weaver and T. Neal Petry. J. Indiana M. A. 51:644-648 (May) 1958 [Indianapolis].

A 28-year-old woman was first seen on March 11, 1956, complaining of swelling and tenderness of her right jaw for 1 day. She was the mother of 3 children, 2 of whom had had mumps 2 weeks before, and the third and youngest was a nursing infant of 11 weeks. She returned 8 days later because her baby had "choked" while nursing. She said that 3 days after the previous visit her breasts had become very tender and swollen, but not hot. In a few days lactation decreased, and the physician thought this accounted for the infant's choking. At the second visit her left parotid was swollen, and she was ordered to cease nursing the child. The administration of stilbestrol, 0.1 mg. daily, was started, and 3 days later lactation had ceased, with caking of the breasts absent 6 days later. The infant was followed closely but manifested no signs or symptoms of mumps.

Although mumps mastitis is a recognized complication of epidemic parotitis, it has been reported rarely. The authors found reports of only 2 other cases, and only 1 of them concerned a nursing mother. Neither the infant of this patient nor the infant of the nursing mother cited had signs of mumps. The immunity existing in infants up to 6 or 8 months of age is generally considered passive immunity from the transfer of maternal antibodies across the placenta. The mothers were not immune in these 2 instances, and presumably the maternal circulation carried no antibodies. Therefore, the mechanism of the immunity displayed by the infants is apparently different. An alternate possibility is that the infants had subclinical mumps. The authors suggest that serologic tests be done on apparently well infants whose mothers have the disease, and that observations be made and reported as to whether nursing mothers with mumps mastitis can nurse after subsequent pregnancies.

Testosterone Pellet Implants for Advanced Breast Carcinomatosis in the Female: Preliminary Report. C. P. Lamar and P. R. Rezek. J. Am. Geriatrics Soc. 6:397-404 (May) 1958 [Baltimore].

The authors report on clinical and pathological observations made during a 10-year period at the Jackson Memorial Hospital, Miami, Fla., on 100 women who were treated by subcutaneous implants of testosterone pellets for palliation of advanced and otherwise intractable breast carcinomatosis. Testosterone (pure crystalline) compressed pellets (75 mg. each) were implanted, 10 at a time, into the subcutaneous fat through a special trocar. Implants were made at weekly intervals for 6 or more times. Then they were spaced farther apart—up to twice a year in a patient who survived for more than 8 years, and 3 to 6 times a year in other patients who survived for periods ranging from 3 to 6 years. Implants of pure testosterone have the advantage of more prolonged effect and less frequent administration than intramuscular injections of testosterone esters. Masculinizing changes seemed to be less conspicuous than with other forms of less intense androgenic therapy. Edema was minimal, and there was no hypercalcemia. In 2 patients

tetanic muscular contractions were relieved by parenteral administration of calcium. As a rule, serum levels of protein, calcium, phosphorus, and alkaline and acid phosphatase remained within normal limits. Exacerbations of neoplastic activity were accompanied occasionally by a transient increase in the serum levels of alkaline and acid phosphatase, and more frequently by an increase in serum protein-bound iodine concentration and radioactive iodine uptake by the thyroid gland along with decreased glucose tolerance. Subjective responses were good in more than 90% of the patients, as manifested by reduction or even suppression of severe pain, production of euphoria, and gain in appetite, weight, and strength. The duration of remissions was variable, averaging 28 months, with a range of 8 weeks to more than 8 years.

The cases of 3 of the 100 patients are described to illustrate some gross and histological changes observed and the relatively low incidence of masculinizing changes. In a patient whose remission has persisted for more than 8 years, mammary biopsy was performed both before and after a radical mastectomy 3 years after onset of therapy. There was gross reduction in the size of the primary breast tumor and lymph nodes, but the histological picture showed no changes. In another patient impressive histological changes took place after androgenic therapy; there was remarkable new epithelization of all ulcerated areas with distinct healing and shrinkage of all lesions. Sex chromatin was observed in some of the tumor cells both before and after treatment; and again at autopsy, after hypophysectomy, sex chromatin was found in the skin, adrenal cortex, and tumor tissue.

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Tuberculosis of the Endometrium: A Report on 250 Cases with the Results of Drug Treatment. A. M. Sutherland. Obst. & Gynec. 11:527-536 (May) 1958 [New York].

Two hundred fifty women, between the ages of 16 and 53 years, with endometrial tuberculosis, were treated at the David Elder Infirmary in Glasgow during the past 7 years. Twenty-eight patients were unmarried, and only 29 gave a history of previous pregnancy. A history of definite or possible extragenital tuberculosis was obtained from 137 of the 250 patients. The interval between the earlier tuberculous manifestations and the discovery of the endometrial infection varied widely but was 5 or more years in most of the patients. Principal symptoms consisted of infertility in 104 patients, abdominal pain in 54, profuse and sometimes irregular bleeding in 41, amenorrhea in 25, and vaginal discharge in 12. Fourteen patients had no complaints. Chest roentgenograms revealed unsuspected active pulmonary lesions in 8 and healed pulmonary lesions in 103. Cervical biopsy revealed unsuspected cervical tuberculosis in 4 patients. A provisional diagnosis of endometrial tuberculosis was based initially on the histological findings in the curettings in most patients. Bacteriological proof was sought in 229, and a positive result was obtained in 170. In 132 of the latter patients, the tubercle bacilli were of the human type. Antituberculous agents were given to 242 patients. Streptomycin and aminosalicylic acid (PAS) were given for 84 days to 152 patients. Of these, 102 (67%) had a persistently negative endometrium after an average follow-up period of 25 months, 32 (21%) had recurrences of the endometrial infection, and 18 were lost to follow-up. Streptomycin and isoniazid were given for 84 days to 69 patients. Fifty-nine patients remained negative after an average follow-up period of 16 months. Recurrences were observed in 6 patients in the second and the third year after treatment. Four patients were lost to follow-up. Aminosalicylic acid and isoniazid were given to 19 patients for 6 to 12 months. It is still too early to compare the results obtained with those in the other groups. Two patients were treated with isoniazid alone, but the use of a single drug is undesirable and this method was abandoned. Recurrences occurred in 40 of the 242 patients, and 22 of the 40 patients were cured after a second course of drug therapy, the average time of follow-up being 22 months. Toxic drug reactions, such as vestibular disturbances, skin rashes, and gastrointestinal disturbances, occurred in 35 (14%) of the 242 patients, requiring discontinuation of therapy in all these patients.

From a consideration of the results of treatment obtained in these patients, it appears that the results obtained are better than those observed in control patients. It is too early to assess the value of streptomycin and aminosalicylic acid as compared with that of streptomycin and isoniazid, although the results to date suggest that the latter combination is at least as effective as the other and is less likely to be associated with toxic drug reactions. The occurrence of major drug reactions in 35 patients is disturbing. Although a few control patients did become negative without chemotherapy, the reported data show that it is not justifiable to withhold treatment from any patient with proved endometrial tuberculosis. Most of the controls remained positive at follow-up, and an appreciable number showed clinical deterioration in the course of the control year and required immediate treatment. In contrast to that, most of the treated patients have been cured of their principal complaints, apart from those with infertility. A continued follow-up of the patients will show whether these conclusions should be modified in the light of further experience.

Postclimacteric and Menopausal Hemorrhages. G. F. Winter, R. Häntsch and P. Rotter-Pool. Ztschr. Geburtsh. u. Gynäk. **150**:19-28. (No. 1) 1958 (In German) [Stuttgart, Germany].

The authors regard as the postclimacteric phase the period between the last menstruation and the definite menopause, defining the onset of the latter as 3 years after the last menstruation. They admit that the definition of these 2 concepts varies in the literature, and since they wanted to compare their findings with those of other clinics, they limit the postclimacteric period in this study to 2 years after the last menstruation. They investigated the postclimacteric and menopausal hemorrhages of patients treated at the University Women's Clinic in Berlin during the 5 years from 1950 to 1954 inclusive. A total of 1,623 patients were involved. It was found that 57.5% of the postclimacteric and menopausal hemorrhages were due to malignant lesions, whereas the average in the world literature is 53.7 or 55.2%. Malignant lesions were the cause of 35% of the genital hemorrhages during the postclimacteric and of 60% of those during the menopausal period, whereas in sexually mature women, up to the age of 45, a total of 15% of the nonmenstrual hemorrhages were due to malignancies. Cervical carcinoma was found to cause 66%, carcinoma of the body of the uterus 22%, and carcinoma of the ovary 5.7% of all the postclimacteric and menopausal hemorrhages that were due to malignant causes.

Studies on the incidence of hemorrhage in the presence of ovarian tumors revealed that 34% were accompanied by hemorrhage, or abut 1 in 3. An ovarian tumor was found, on the average, in 1 woman in 17 with postclimacteric or postmenopausal hemorrhages. Cervical polyps were the most numerous among the nonmalignant lesions responsible for genital hemorrhages, accounting for 16.2% of the postclimacteric or menopausal hemorrhages traceable to benign causes. One of 3 "benign" postclimacteric hemorrhages originated in the endometrium under hormonal stimulus, whereas only 1 in 9 of the menopausal hemorrhages was due to this cause. In 40% of all the women with bleeding from a hormonally activated endometrium, the history revealed treatment with estrogens. The percentage was even higher (50%) when the women were questioned regarding the use of hormone ointments and creams. Myoma, which together with glandular hypertrophy is the most frequent cause of hemorrhages during the climacteric, plays only a subordinate role in this respect during the postclimacteric period and during the menopause, accounting for 6.2% of benign and for 2.6% of all hemorrhages.

PEDIATRICS

Serum Oxaloacetic Transaminase Activity in Acute Rheumatic Fever: Values in Cases With and Without Salicylate Therapy. R. W. Massie and M. Stahlman. A. M. A. J. Dis. Child. **95**:469-476 (May) 1958 [Chicago].

Eighteen patients with acute rheumatic fever were studied over long periods with serial determinations of serum glutamic oxaloacetic transaminase (SGOT) activity, C-reactive protein (CRP), antistreptolysin-O (ASO) titer, and erythrocyte sedimentation rate (ESR). SGOT activity was elevated in some patients with acute rheumatic fever. These elevations were inconstant, however, and equally ill patients sometimes showed no elevation. Elevated values of SGOT occurred only in the patients with active rheumatic carditis. Rheumatic carditis was frequently not accompanied by elevation in SGOT. A single determination of SGOT activity was of little value in diagnosing acute rheumatic fever or in following the course of the disease. Some values that were not above the "upper limit of normal" were demonstrated to be significantly elevated when serial determinations were performed. A rise and fall in SGOT values were often well correlated with ESR, CRP, and ASO-titer determinations as well as with the clinical status of the patient. Administration of acetylsalicylic acid did not affect SGOT activity in the absence of active rheumatic carditis. The effect of salicylates on SGOT activity in the presence of active rheumatic carditis was uncertain, and inconstant results were obtained in several patients.

Bilateral Choanal Atresia, a Surgical Emergency in the Newborn. R. C. Morrow. J. Maine M. A. **49**:135-136 (April) 1958 [Brunswick].

Some cases of neonatal asphyxia are due to undetected bilateral congenital atresia of the posterior nares. The author presents observations on 4 infants with bilateral atresia observed at the Mary Fletcher Hospital in Burlington, Vt., and reviews the recent literature on this problem. The fact that the 4 cases were observed in 3 years suggests that this defect cannot be regarded as rare. The persistence of the nasobuccal membrane, which normally ruptures in the 7th week of fetal life, is the most widely accepted embryologic mechanism of this anomaly. The newborn infant is often unable to survive nasal obstruction, as though it were not instinctively aware of the simple expedient of breathing through the mouth. The clinical picture is that of obstructed breathing, with the varying degrees of intermittent success in getting a little air through the mouth. Usually the infant can be kept breathing by any expedient which serves to

hold the mouth open and the tongue down and forward. Feeding is difficult, because sucking, swallowing, and breathing cannot be carried on simultaneously. Even infants who can achieve mouth breathing are in danger of death by starvation. Once the condition is suspected, the diagnosis can be clarified by attempting to pass catheters through the nasal cavities into the pharynx, and by obtaining x-ray films with the instillation of contrast media into the nostrils.

Every breath of the infant should be supervised until adequate surgical relief is achieved. The mouth can be kept open by means of a small oral airway of the type used in anesthesia. The surgical management is early penetration of the choanal obstruction. Three of the 4 newborn infants with bilateral choanal atresia observed by the author were operated on, on the 1st, 2nd and 16th day of life respectively. The 4th infant had, in addition, multiple anomalies of the heart and great vessels and died on its 9th day. The choanal problem was recognized, and, by constant nursing attention, oral breathing and adequate feeding were being maintained, while corrective surgery was to have been done had the infant survived its cardiac anomalies a few more days. The 3 infants responded well to prompt operation in the newborn stage, followed by a program of periodic dilatations and the intermittent use of polyethylene breathing tubes. The possibility of bilateral choanal atresia should be thought of in threatened neonatal asphyxia.

Acute Cerebellar Ataxia of Childhood: Report of 9 Cases. G. King, G. A. Schwarz and H. W. Slade. Pediatrics **21**:731-745 (May) 1958 [Springfield, Ill.].

The authors report on 6 boys, between the ages of 2½ and 11 years, and on 3 girls, between the ages of 17 months and 3 years, with acute cerebellar ataxia. The neurological sign of most clinical significance was the ataxic gait. This occurred in varying degrees of severity in 8 of the children. Truncal ataxia, action tremor, and dysmetria were also frequently noted, but nystagmus, hypotonia, and hyporeflexia were infrequently observed. Choreiform movements and hemiparesis with hyperreflexia occurred in a few patients and indicated that the pathological process was not limited to the cerebellum in these patients. Fever was present in 5 patients. Seven of the patients had some degree of disturbance of personality and state of consciousness as part of the illness. The most pressing diagnostic problems presented were the degree of increased intracranial pressure and the possibility of a neoplasm of the posterior fossa. Changes of the optic nerve heads in 4 patients and bilateral early evidence of papilledema in 2 were suggestive of increased intracranial pressure. The indications were such that ventricular tap and ventriculography were performed in 5 of the 9 patients; in none of them was the intraventricular pressure increased. Five patients made a complete recovery. Residual disturbances in behavior were observed in 4 children: there was simple retardation in 1 and a schizoid personality change requiring institutionalization in another; in the remaining 2, only mild apathy and irritability at school were reported. The causation was not determined in any of the 9 patients. The children were quite healthy when the acute ataxia began, and none of them had a history of head trauma or preceding infection. Four of the patients had the onset of their illness in the months from January through March, and 5 in the months from August to October; these findings might suggest that these cerebellar disorders of childhood are due to different seasonally prominent pathogens.

Similar cases were collected from the literature, which had been recorded as "acute cerebellar encephalitis" or "acute cerebellar ataxia," a form of nonsuppurative encephalitis. The concept is proposed that these cases represent a toxi-infectious process of variable causation with the cerebellum or its systems as the major or only target organ. The main significance of these relatively benign forms of cerebellar disorder in children is their differentiation from cerebellar tumor. In the cerebellar medulloblastoma, the course is inevitably progressive with increasing papilledema or hydrocephalus. In acute idiopathic cerebellar disorders, the papilledema does not increase; there is usually no progression of signs, and in several weeks the signs begin to recede. A careful, watchful waiting would seem to be the best procedure in such cases, but ventricular tap and ventriculography may be the methods of choice in settling the diagnostic problem finally.

Multiple Sclerosis in Children: A Clinical Study of 40 Cases with Onset in Childhood. J. C. Gall, A. B. Hayles, R. G. Siekert and H. M. Keith. Pediatrics **21**:703-709 (May) 1958 [Springfield, Ill.].

The authors studied 26 girls and 14 boys with disease of the central nervous system, characterized by several attacks of neurological dysfunction and disseminated lesions, with onset in childhood and clinically typical of multiple sclerosis. In 8 of the 40 patients who were admitted to the Mayo Clinic between 1920 and 1952, the age at the onset of the disease was 10 years or less, and in the remaining 32 it was between 11 and 14 years. The disease as it occurred in these children did not appear to differ clinically from the disease as observed in adults, in respect to mode of onset, symptoms, physical findings, and changes in the cerebrospinal fluid. In contrast, however, to the equal occurrence of multiple sclerosis in men and women according to reports on adults by other workers, the girls predominated among these chil-

dren in a ratio of 2:1. Follow-up data were available by letter on 32 patients; 10 were still ambulatory, 10 were bedfast, and 12 had died. Death presumably resulted from multiple sclerosis or its complications. The youngest patient to die was 16 years old. A pediatrician confronted with a child showing evidence of scattered neurological deficits that remit, particularly a disturbance of vision and coordination, should consider the possibility of multiple sclerosis.

Acute Epiglottitis in Childhood: A Serious Emergency, Readily Recognized at the Bedside. W. Berenberg and S. Kevy. New England J. Med. **258**:870-874 (May 1) 1958 [Boston].

The authors report on 26 boys and 16 girls, between the ages of 3 months and 14 years, with epiglottitis, who were admitted to the Children's Medical Center in Boston between 1946 and 1954. The onset of the disease was abrupt, and in 39 patients the initial complaint was one of difficulty in breathing. In patients who were able to express themselves, extreme pain in the throat was impressive and usually associated with marked dysphagia. There was a striking retention of secretions, with visible and copious puddling of pharyngeal mucus in 20 patients. Irritability and marked restlessness appeared fairly early. Hoarseness was present in 12 patients at the time of admission to the hospital. Definite stridor occurred in 30 children. A croupy crow was described in 15. Temperatures ranged between 100 F (37.7 C) and 105 F (40.5 C), with an average of 102.5 F (39 C). The respiratory rates varied between 22 and 60 respirations per minute. There was definite involvement of the epiglottis in all the patients. Although this varied somewhat in severity and in the apparent degree of inflammation, constant features were edema and a striking, fiery-red appearance, so that on depression of the tongue and examination of the pharynx, a "cherry-red" epiglottis came into view of the examiner. Diminished breath sounds indicated poor air exchange in 24 patients. A history of prostration and marked respiratory obstruction was obtained in the 3 patients who were found to be dead on arrival at the hospital. Two additional children died within 3½ hours after admission.

Blood cultures were obtained in 16 of the 39 patients who were alive at the time of admission to the hospital. Positive cultures for Hemophilus influenzae, group B, were obtained in 11 of the 16 patients. One blood culture yielded pneumococci. Throat culture yielded H. influenzae, group B, in 17 patients and a hemolytic Staphylococcus pyogenes var. aureus in 2. Direct cultures from the epiglottis at the time of tracheotomy, which was carried out on 18 patients as a lifesaving measure, yielded pneumococci in 1 patient, beta-hemolytic streptococci in 1, and H. influenzae, group B, in 11. Penicillin and streptomycin were given to 16 patients, penicillin, sulfadiazine, and streptomycin to 10, streptomycin and sulfadiazine to 5, penicillin, streptomycin, and chloramphenicol to 2, penicillin and sulfadiazine to 1, penicillin and chloramphenicol to 1, all four agents to 1, and chlortetracycline and chloramphenicol to 1. Penicillin and streptomycin were administered intramuscularly for 24 hours, and then orally as soon thereafter as the patient could tolerate that route. Sulfadiazine was given orally, subcutaneously, and, to 3 patients, intravenously.

Acute epiglottitis is a serious and often fatal condition that, although infrequently recognized, lends itself to accurate bedside diagnosis with consequent institution of specific lifesaving therapy. Its recognition and management should become familiar to all concerned with the care of sick children. The reported data emphasize the importance of H. influenzae, group B, as the predominant but not the only micro-organism producing this clinical picture, and the lifesaving value of tracheotomy to relieve the rapidly developing obstruction of the upper airway. The chemotherapeutic agent of choice is chloramphenicol in doses of 100 mg. per kilogram of body weight given intravenously for the first 24 to 36 hours and then reduced to 50 mg. per kilogram orally if it is tolerated.

Diabetes and Growth in Children: Comments on the Mauriac Syndrome and Its Treatment. H. Lestradet. Presse méd. **66**:582-584 (April 2) 1958 (In French) [Paris].

The appearance of a significant insulin deficiency in children during the period of growth may give rise to clinical manifestations which should be given individual consideration. One of these clinical forms, presented only by patients capable of significant adrenocortical response, is the Mauriac syndrome, in which retardation of growth may or may not be associated with evident signs of hypercorticism. Retarded growth and delay in puberty in juvenile diabetic patients, however, should be ascribed solely to nutritional deficiency and to a poorly regulated insulin therapy, and not to a metabolic derangement peculiar to the disease itself. In some of the author's patients with the Mauriac syndrome, a slight increase in the dietary supply of glucides was followed by a dramatic regression of hepatomegaly, resumption of growth, and a rapid onset of puberty.

Treatment then consists of (1) a normal, well-balanced diet, with a sufficient supply not only of proteins and vitamins but also of glucides, and (2) a well-supervised insulin therapy. Twice the average dose of insulin required by diabetic adults may be needed by children with diabetes, if they are to have a satisfactory physiological development during the period of puberty. Thereafter these large

doses of insulin can be reduced, sometimes rapidly, to those usually regarded as normal in adults. Regular insulin is sometimes poorly tolerated by children with the Mauriac syndrome. Thus, no improvement was obtained from total doses of 120 to 140 units of regular insulin administered in 6 injections daily to a 10-year-old boy in whom ketosis and hypoglycemic reactions occurred alternately. The administration of 2 injections daily of 30 to 40 units (one-third of the previous dose) of protamine zinc insulin, however, resulted in the immediate disappearance of ketosis and hypoglycemia, while at the same time the hepatomegaly disappeared and growth was resumed. Six months later this patient had grown 6 cm. (about 2½ in.) in height, and the usual treatment with a mixture of regular insulin and protamine zinc insulin administered in a single injection in the morning could be resumed. Delay in growth, whatever clinical aspect it assumes as a result of individual hormonal reactivity and of the degree of insulin insufficiency, should disappear completely if children with diabetes are treated according to physiological therapeutic principles, i. e., if they are given a rational diet and insulin therapy adapted to their needs, which are generally great during the period of growth.

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Intestinal Diseases After Antibiotic Therapy: Clinical and Bacteriological Aspects of Bacterial Superinfection After Treatment with Broad-Spectrum Antibiotics. G. Möbius, L. Möbius and L. Weingärtner. Ztschr. Kinderh. **80**:615-641 (No. 6) 1958 (In German) [Berlin].

The authors list 5 groups of secondary effects that may occur after treatment with broad-spectrum antibiotics, particularly after penicillin, streptomycin, chloramphenicol, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin). These are (1) toxic effects, (2) allergic complications, (3) damage to the hematopoietic system, (4) bacteriolysis-induced secondary effects resembling the Herxheimer reaction during syphilis therapy, and (5) complication resulting from effects on the physiological bacterial flora in the respiratory or intestinal tracts. This paper is especially concerned with observations on 13 children, in whom serious intestinal disturbances developed during treatment with broad-spectrum antibiotics. High temperatures, watery stools, and vomiting occurred from 4 to 11 days after onset of the antibiotic therapy. All except 1 of the children were less than 2 years, and 7 were less than 1 year old. Eight of the children died, and 5 survived. All except 1 child had been treated with chloramphenicol, a few had received penicillin or chlortetracycline in addition, and 1 had received only chlortetracycline. The feces or intestines of all the children contained resistant staphylococci, and in 2 of the infants who died pathogenic fungi (Candida and Aspergillus) were found in addition.

On the basis of clinical, bacteriological, and pathological investigations on the 13 patients and of a review of literature reports, the authors emphasize that intestinal disorders after treatment with broad-spectrum antibiotics are to be characterized as superinfections, which are produced most frequently by staphylococci that are resistant to antibiotics and occasionally by saprophytes that may become pathogenetic or by fungi. The causal organism that is resistant or not responsive to antibiotics originates in the physiological, oral, or intestinal floras, in which it becomes dominant and unrestrained after the selective elimination of susceptible organisms. The resistant staphylococci are often transmitted to the patient within the hospital, because here they are usually predominant. While the pathological changes in the intestine vary, they are usually characterized by a pseudomembranous inflammation. As an unexpected and hitherto not described finding, the authors observed in 3 of the children severe edema in the cecum, which on histological examination was found to be restricted to the submucosa, where it had caused extensive dissolution of fibers. This tissue-destructive edema is regarded as a manifestation of a disturbance in permeability with formation of an exudate high in protein content and with fermentative effect. The effect of the intestinal disorder on the body in general usually becomes evident in symptoms of the central nervous system. Edema of the brain, central follicular necrosis of the spleen, and fatty degeneration of the liver are generally found and are attributed to the action of staphylococcic toxins. However, septicopyemia could be excluded in the reported cases.

Retrolental Fibroplasia: A Case Report on Preventable Blindness. W. H. Havener. Ohio M. J. **54**:496 (April) 1958 [Columbus].

The boy whose history is presented weighed 3 lb. 15 oz. (1,800 Gm.) at birth, the estimated length of pregnancy being 7 months. Oxygen was given for 3 days in unknown concentration. Although both eyes were normal shortly after birth, at the age of 6 months this child had markedly impaired vision. Reexamination at this time showed traction bands which displaced the large central retinal vessels. Fibrovascular membranes swept across the macular area, obviously destroying central vision. Retrolental fibroplasia occurs almost exclusively in premature infants who have received supplemental oxygen. Central vision may be destroyed by fibrovascular membranes, as in this case, or the whole retina may become detached and pulled forward to produce the "retrolental" membrane. No therapy is known to be effective once the disease has manifested itself. It is extremely hazardous to use oxygen in the care of premature infants, except when obvious cyanosis or other evidence of anoxia exists.

THERAPEUTICS

Acute Glutethimide (Doriden) Poisoning: The Use of Bemegride (Megimide) and Hemodialysis. G. E. Schreiner, L. B. Berman, R. Kovach and H. A. Bloomer. A. M. A. Arch. Int. Med. **101**:899-911 (May) 1958 [Chicago].

Glutethimide has been used widely as an hypnotic and a sedative. Chemically, glutethimide is α-ethyl-α-phenylglutarimide. While working with a new barbiturate antidote, β-methyl-β-ethylglutarimide, known as bemegride (Megimide), the authors were impressed by the clinical similarity and disparate pharmacology of α-ethyl-α-phenylglutarimide, the depressant, and β-methyl-β-ethylglutarimide, the stimulant. Shortly thereafter they had the opportunity of contrasting the response to glutethimide in barbiturate poisoning to the clinical response in a patient who was admitted with presumed barbiturate intoxication but proved subsequently to have negligible amounts of barbiturate and a substantial concentration of glutethimide in the serum. The authors describe their observations on 6 patients with severe glutethimide poisoning whom they treated with varying combinations of supportive measures, bemegride, and external hemodialysis. There was 1 fatality. The first patient, who had severe poisoning from the ingestion of 7.5 Gm. of glutethimide responded dramatically to bemegride. The second patient, who presumably had taken approximately 10 Gm. of glutethimide and possibly a small amount of secobarbital (Seconal), also responded immediately to bemegride. The depression of respiratory rate in this patient was extreme. It may have been related to the associated barbiturate intake or to the ingestion of alcohol or some other unknown drug.

The 3rd patient was admitted unresponsive after the ingestion of 10 Gm. of glutethimide. She also had taken alcohol and possibly other drugs. This patient died. A surprise finding at autopsy was the presence of a massive coronary atherosclerosis, which must be considered most unusual in a 24-year-old woman. The authors wonder whether circulatory impairment could have contributed to her death. The 4th patient had marked hypotension, even after return of a reasonable degree of consciousness in response to bemegride. There was also the possibility of chronic cumulative toxicity of glutethimide, since she appeared groggy before her acute ingestion. She demonstrated apnea on manipulation. Anoxemia worsened the coma, and this patient might not have survived without hemodialysis, which reduced the blood glutethimide level. Patients 5 and 6 were treated with bemegride, and in the latter hemodialysis was also used. The authors stress the difficulties of treating patients poisoned by drugs. The great variety of tranquilizing drugs and the numerous hypnotics and sedatives produce a great multiplicity of possible interrelationships of drug effects. The toxicologist dealing with patients must take cognizance of such factors as inaccurate history of dosage, ratio of ingested dose to absorbed dose, time elapsed before treatment, underlying physical state, and individual drug tolerance.

The authors define the bemegride-glutethimide relationship as a functional antagonism. Bemegride stimulates the respiratory and circulatory center and restores reflexes and consciousness. However, the drug also produces exaggerated reflexes, muscle twitching, tremor, clonus, hyperventilation, and epileptic potentials in the electroencephalogram. Discussing a therapeutic plan for acute glutethimide intoxication, the authors show that, in patients with the mild form, symptomatic therapy and patience are enough. In patients with a moderate degree of intoxication, treatment should include lavage of the stomach. The use of endotracheal suction and oxygen and pressor drugs for hypotension are valuable, but care is necessary to avoid overhydration. Cerebral edema represents a major threat. It is well to be suspicious if more than 1,500 mg. of bemegride is required to lighten anesthesia. The administration of bemegride should be stopped immediately if clonus or convulsions are produced. Patients with severe glutethimide intoxication should be titrated with bemegride immediately after a sample has been taken for the determination of glutethimide blood level before bemegride is given. In the event of failure to elicit a light reflex or plantar withdrawal, a bemegride requirement greater than 1,500 mg. on titration, convulsions from bemegride, or later deterioration of the clinical state, plans should be made for external hemodialysis.

On the Mechanism of the Diuretic Action of Chlorothiazide in Human Beings. V. Bonomini and P. Zucchelli. Policlinico (sez. prat.) **65**:487-496 (March 31) 1958 (In Italian) [Rome].

Diuretic action of chlorothiazide was studied in 19 patients of both sexes, between the ages of 19 and 68 years. Cardiovascular or renal disorder was present in 9 patients, cardiac decompensation of the congestive type in 6, and edema in the lower extremities ascribed to chronic kidney disease but unrelated to hyperazotemia in 4. Chlorothiazide was administered intravenously in a single injection, varying from 100 to 500 mg., without causing toxicity. Chlorothiazide produced an increased urinary output in patients with cardiovascular disorders, but only a slight effect in patients with a renal disorder. Larger doses of the drug had an effect on duration of the action rather than on its intensity. Chlorothiazide did not affect either the glomerular filtration rate or the renal blood flow. The drug exerted its diuretic effect only through

the tubular action. Like mercurial diuretics, chlorothiazide blocked the reabsorption of sodium chloride. The drug also produced an increased excretion rate of phosphate, bicarbonate, and sodium chloride. It caused a decrease in both ammonia and titratable acidity excretions. The pH of the urine increased in patients with cardiovascular decompensation, but it did not change much in patients with severely damaged renal tubules. Diuretic response to chlorothiazide resulted from blockage of sodium chloride reabsorption in the renal tubules. This study confirms the effective diuretic action of chlorothiazide in human beings.

Sodium Balance During Prednisone Treatment. S. Gjørup and J. H. Thaysen. Ugesk. læger **120**:471-476 (April 10) 1958 (In Danish) [Copenhagen].

Prednisone is not suitable as the only substitution therapy in Addison's disease. It is particularly adapted for long-term treatment in cases where cortisone has caused troublesome fluid retention or where cortisone has been regarded as contraindicated because of edema or tendency to edema. No potassium addition should be given during treatment with prednisone. Although with the usual doses applied in the treatment of chronic polyarthritis and with free choice in diet the development of a salt-poor syndrome is hardly to be feared, the possibility should be borne in mind if fall in blood sugar, shock, and so on suddenly occur in patients treated with massive prednisone doses. This applies especially if the patient's salt intake is simultaneously reduced. In stress situations patients with secondary insufficiency of the adrenal cortex as the result of long-continued prednisone treatment should receive the addition of cortisone or hydrocortisone.

Pancytopenia and Granulocytopenia After Carbutamide in Diabetes. S. Aarseth and H. Willumsen. Nord. med. **59**:564-565 (April 17) 1958 (In Norwegian) [Stockholm].

Three cases of hemorrhagic complications on carbutamide treatment are reported, 2 with fatal outcome. Diabetes mellitus developed in a man, aged 81 years, who had previously been well. Carbutamide was given in the usual therapeutic doses of 28 and 13 Gm., with an interval of 6 months. There was progressive bone marrow depression, with anemia, thrombocytopenia, and total disappearance of white blood corpuscles. Death occurred 12 days after the carbutamide was withdrawn. In the second case, in a woman, aged 70, with long-continued heart disease and recently diagnosed diabetes mellitus, polyclinical treatment with carbutamide in the usual doses was effective in reducing the blood sugar. After 4 weeks general dermatitis and fever set in, with almost total disappearance of neutrophil granulocytes. The patient died. The total carbutamide dose was 43 Gm. in 7 weeks. The third patient, a man, aged 68, with moderate diabetes of 3 years' standing, was treated with a total of 30 Gm. of carbutamide in the course of 4 weeks. Because of fever and diarrhea the treatment was discontinued; another not readily resorbable sulfonamide was given for a couple of days. Examination of the blood showed anemia and complete granulocytopenia. The patient recovered after massive doses of penicillin and blood transfusions. Carbutamide involves a not inconsiderable risk of hematological complications threatening life, especially granulocytopenia. Since similar complications have not been observed on tolbutamide treatment, and since the effect in reduction of blood sugar is the same as that of carbutamide, carbutamide therapy should not be employed in the treatment of diabetes.

PATHOLOGY

The Spread of Lung Cancer to the Brain. W. I. B. Onuigbo. Brit. J. Tuberc. **52**:141-148 (April) 1958 [London].

It is a striking feature of lung cancer that brain and adrenal metastases frequently coexist. In a previous paper the author had demonstrated that the topographic distribution of adrenal deposits accords well with lymph-borne and not artery-borne metastasis. This finding posed the question of whether a similar pattern was demonstrable in the case of brain secondaries. Because it has been denied that the brain has lymphatic connections, the current view is that lung cancer metastasizes to this organ via the arteries. Theoretically, arterial scattering of tumor emboli should result in an even distribution of deposits on either side of the brain. Lymphogenous dissemination to the brain, however, would lead to ipsilateral preponderance of deposits. The author reviewed cases of bronchial carcinoma from the autopsy records of the Scottish Medical Schools and the Stobhill General Hospital, Glasgow. In every case showing unilateral metastases in the cerebral or cerebellar hemisphere, it was noted whether the deposits were ipsilateral or contralateral. For bilateral metastases, the side containing the larger deposits was similarly noted.

Two hundred fifty cases fulfilling these criteria were analyzed. Of 177 patients showing unilateral deposits, 100 were ipsilateral and 77 were contralateral; of 73 patients showing bilateral growths, 43 contained the larger deposits ipsilaterally and 30 did so contralaterally. Thus, in the whole series of 250 cases, ipsilateral tendency was exhibited on 143 occasions, and the contralateral trend was manifest 107 times. This finding is statistically sig-

nificant and is in keeping with lymphatic metastasis. Fifty-five cases collected from the literature also exhibited a statistically significant ipsilateral preponderance. Other factors indicating that the spread of lung cancer to the brain takes place by way of the lymphatics, rather than the arteries, are as follows: 1. Subdiaphragmatic tumors metastasize to the brain more often than do infradiaphragmatic tumors. 2. The relatively nearer cerebellum is a site of metastatic predilection. 3. The outstanding histopathological features of brain metastases include the common finding of tumor cells in perivascular spaces and the difficulty of demonstrating them inside vessels. Two controversial questions are asked. First, do lymphatics effect connections with these perivascular spaces? Many anatomists thought so. Secondly, are the subarachnoid spaces and the lymphatic system connected? Indian ink introduced into the cranial subarachnoid appeared within 4 hours in cervical nodes and ultimately in intrathoracic nodes.

Rheumatic Fever and Rheumatic Heart Disease: II. Life Expectation and Natural History. E. Waaler. Acta med. scandinav. **160**:293-303 (No. 4) 1958 (In English) [Stockholm].

The authors report on 211 patients who died at the University Hospital in Bergen, Norway, between 1941 and 1955 and in whom a diagnosis of rheumatic heart disease was made on autopsy. History revealed rheumatic fever in 46 (60%) of the 76 men and in 61 (45%) of the 135 women. This higher incidence of rheumatic fever in men, as compared with women, was not apparent in the younger age groups, but it was significant in the older age groups. Chronic valvular disease was recorded as the cause of death in patients whose average age was 52 or 53 years at the time of death. Death occurred at an earlier age in patients with bacterial endocarditis than in those with pure rheumatic lesions. The average interval between the first attack of rheumatic fever and death was 30 to 32 years in patients dying of chronic valvular disease. The mean age at death was strikingly higher in these patients than in those whose cases were collected from the United States literature. It seems that rheumatic fever and rheumatic heart disease have had a milder course in Norway than in the northeastern part of the United States. The difference may be partly due to the fact that the patients in Norway were less selected, but it must also be remembered that rheumatic heart disease in more recent years has had a tendency to run a milder course than in the years between 1900 and 1920, the period with which the American studies were concerned.

Acute rheumatic fever occurs mainly in children and adolescents. A severe valvular lesion is more likely to occur in patients with rheumatic heart disease and a positive history of rheumatic fever than in those with a negative history of rheumatic fever. Rheumatic heart disease acquired in childhood and adolescence takes a more severe course than that starting in adult life. The findings in the 135 women also indicated that in adult life the silent insidious types of rheumatic heart disease are particularly common in women. The preponderance of women among the 211 patients is partly due to the fact that women are apparently more susceptible to the hyperergic inflammatory type of reaction than men. Microscopic evidence of active rheumatic inflammation was found in only 5 men and 9 women with chronic disease, but the small number of patients does not permit any conclusions concerning a possible difference between men and women. This low incidence of activity on microscopic examination is probably partly due to the fact that 34 of 92 patients who died of chronic valvular disease were above 60 years of age. The longest interval between clinical signs of activity and microscopic findings of activity was 35 years. The clinical ability to make a diagnosis of activity of rheumatic heart disease seems to be lacking, and inflammatory scarring of the valves may take place without being revealed by definite clinical signs.

Presence of Neoplastic Cells in the Peripheral Arterial Blood of Patients with Bronchial Cancer. C. Colombo, G. Maggi and F. Rolfo. Minerva med. **49**:725-730 (Feb. 28) 1958 (In Italian) [Turin, Italy].

Peripheral arterial blood of 13 patients with bronchial cancer was investigated for possible presence of neoplastic cells. Specimens of 5 cc. of serum were obtained from the femoral arteries before the surgical operations. Tumor cells were found in the serum of 2 patients. The first patient was a 56-year-old man who had a squamous tumor in the right main bronchus, with diffusion in the carina and metastases in the hilar lymph nodes during a period of 8 months. Sixteen tumor cells were found in his peripheral blood. After he underwent pneumonectomy, histological examination revealed malignant infiltration of the wall of a large thrombotic vein, with invasion of tumor cells into the vessel's lumen. The second patient was a 59-year-old man who had a tumor in the upper part of the left bronchus, which could not be reached by forceps. Bone metastases were roentgenologically visible. Five tumor cells were counted in the peripheral blood. Tumor cells in the peripheral arterial blood of these patients were 2 to 4 times larger than neutrophils and were round or egg-shaped. They had a large cytoplasm clearly outlined, were slightly eosinophilic, and had no granulation. Nuclei were large, some of them vesical, with spots of chromatin which were arranged irregularly. Nucleoli were identifiable and in some instances well marked.

BOOK REVIEWS

Rehabilitation of the Cardiovascular Patient. By Paul Dudley White, M.D., Howard A. Rusk, M.D., Professor and Chairman, Department of Physical Medicine and Rehabilitation, New York University–Bellevue Medical Center, New York, Philip R. Lee, M.D., and Bryan Williams, M.D., Clinical Instructor in Medicine, University of Texas, Southwestern Medical School, Dallas. Cloth. $7. Pp. 176, with 31 illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E. C. 4, England; 253 Spadina Rd., Toronto 4, Canada, 1958.

With the control of acute infectious diseases and the longer life span, chronic degenerative disease of which cardiovascular disease is the most important becomes a major problem not only medically but sociologically. This book shows how patients who have suffered a myocardial infarction or hemiplegia or who have rheumatic heart disease can be rehabilitated and made useful happy citizens. Although the rehabilitation of the cardiac patient has received attention only within the past 10 to 15 years, enormous strides have been made and the techniques described in this book have produced results in many patients who would have ordinarily been consigned to hopeless invalidism. The patient with hemiplegia can also be helped materially, and this book shows how. This small volume should be in every physician's library for ready reference.

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On the Utility of Medical History. Iago Galdston, M.D., editor. Monograph I, Institute on Social and Historical Medicine, New York Academy of Medicine. Cloth. $2. Pp. 73. International Universities Press, Inc., 227 W. 13th St., New York 11, 1957.

This volume is the first of a new series of monographs published by the Institute on Social and Historical Medicine. The purpose of this organization is "to inquire whether medical history can in effect serve to illuminate current problems and issues in medicine. Can they, when seen in the perspective of historical data and historical derivations, be better understood? Can the knowledge of past experiences, historically comprehended, sharpen judgment as to the values and the probable effectiveness of proposed actions?" The book could well have been subtitled, *Apologia pro historia medicinae*. Many pages are devoted to justify the serious study of medical history in the face of a widespread apathy on the part of the medical profession. Thus, for example, Ackerknecht describes the state of medical history courses in medical schools while Schrecker defends the position that we can learn something from history by showing the mutually beneficial relationship existing between the systematic and the historical approach to an area of knowledge. Temkin inquires into the nature of medical historiography, and Zilboorg presents a brief analysis of "the emotional changes of the period that do not permit people to investigate things properly." The practicing physician, the medical student, and others professionally concerned with medicine who read this book should take with them the realization that something good may be said for medical history.

Textbook of Gynecology. By John I. Brewer, B.S., M.D., Ph.D., Professor of Obstetrics and Gynecology, Northwestern University Medical School, Chicago. Second edition. Cloth. $15. Pp. 742, with 204 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This edition, like the first, is designed for use by undergraduate students "to prepare them for the general practice of medicine." Details are reduced to a minimum, although one gets the impression that the author's enthusiasm overcomes his reticence at times. There has been extensive revision of the first edition. An excellent chapter on endocrinology has been added by DeCosta. This describes in some detail the sex abnormalities of development in a clear and authoritative manner. This new edition repeats the division into two parts. In the first, the whole of gynecology is approached from the point of view of symptoms. In the second, the field is re-covered on the basis of organs and their diseases, in so far as possible. The author recognizes that this leads to some repetition. It also makes for a scattering of information throughout the book and probably for reduction of details because of space limitations. This is an excellent approach in talking to students but leaves something to be desired in the use of the book for reference. The book is printed on attractive paper which magnificently shows up the multiple photomicrographs and other illustrations. Typographical errors have been held to a minimum, and a useful index is appended. This is an excellent introduction to gynecology for the undergraduate.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUESTIONS AND ANSWERS

EXAMINATIONS FOR SCHOOL CHILDREN

To the Editor:—*In a fairly well-to-do suburb, private physicians are requested to include in physical examinations for elementary school children a tuberculin patch test, hemoglobin level estimation, and urinalysis for all, including those who are apparently healthy and asymptomatic. Opinions as to the needs and merits are divided. Please comment on this practice.*

H. H. Neumann, M.D., Elmont, N. Y.

Answer.—The tuberculin test is highly recommended as a periodic procedure for all children after the age of two months and for as long as no reaction is elicited. This is the earliest method by which tuberculosis can be diagnosed. It is important to detect this disease, if it occurs, as early as possible in the child's body. Since 1912 it has been known that the child who reacts to tuberculin has tuberculous lesions. Ghon established this fact by meticulous postmortem examinations of the bodies of 184 children who during life had no evidence of tuberculosis except the tuberculin reaction. He found lesions in 183; the body of the remaining child was not completely examined. While these lesions are usually too small to be detected by physical examination, including inspection of the chest by x-ray film, they are nevertheless potential sources of gross clinical disease. A child who becomes a reactor to tuberculin has been in close contact usually with an adult, such as a parent, grandparent, or someone else who has contagious disease. Seeking the source of the infection among adult associates is a most valuable clinical case-finding method. Obviously, the earlier the infection in the child is found, the better are the results for the child. Moreover, the earlier the responsible case is detected, the fewer other persons will be infected and the better the individual's chance of recovery will be. With the advent of antituberculosis drugs, the importance of finding the diseased child soon after the infection has occurred is increased. A great many recent tuberculin converters are now being treated with these drugs. Those currently available apparently are not germicidal, but they suppress tubercle bacilli. Although they do not cure, there is some evidence that they may occasionally prevent the development of acute forms, such as miliary disease or meningitis. If a germicidal drug becomes available the importance of finding the infection early is obvious. Then the lesions are microscopic and vascular; the drug may be expected to enter so as to come in contact with all tubercle bacilli. However, as time passes tuberculous lesions often lose their blood supply, after which a drug could not be expected to reach the organism in avascular necrotic tissue. In most parts of the United States, the number of children who develop tuberculosis so as to become reactors to tuberculin is quite small, often not more than 2 or 3% during the grade-school period, and in some places none do so. Control of tuberculosis among the cattle herds, isolation of persons in sanatoriums, and treatment of others has so reduced the populations of both the human and bovine types of tubercle bacilli that the situation is in sharp contrast with that of a few decades ago, when so many became infected during the period of childhood. There is a high incidence of tuberculosis among persons 40 years of age or older, as manifested by the tuberculin reaction. Some of these older persons become contagious unknowingly and disseminate tubercle bacilli to children. In addition to keeping all older tuberculin reactors under periodic examination, children everywhere should be tested periodically to make certain that those who may be infected from unsuspected sources are detected promptly. Urinalysis and hemoglobin level estimation are important routine procedures, but they do not have the significance that the tuberculin test has with reference to schools and communities.

VISION SCREENING IN SCHOOLS

To the Editor:—*Please supply some information on the current methods for visual screening examinations in school children. What should the standard procedure be, and by whom should the children be examined at the school?*

S. Henry Thaler, M.D., Huntington, N. Y.

Answer.—The Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association has made definite suggestions on vision screening in schools in its second edition of "Health Appraisal of School Children" as follows: "Emphasis must be placed on the fact that school tests for visual acuity are screening tests and are not intended to diagnose the nature of eye defects. They reveal that a child does not see well, but the presence or absence of visual defects requiring correction cannot be determined entirely on the basis of screening tests.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

Screening tests should, therefore, be the province of teachers, nurses, or technologists and not of eye physicians. The most commonly used visual screening procedure is to test with the Snellen chart, at 20 feet under proper lighting, or with the Massachusetts Vision Test based upon the Snellen chart." The details of the testing procedure, including preparation of pupils, arrangement of room and equipment, and referral of children for eye examination, are given in "Health Appraisal of School Children," which may be obtained from the Bureau of Health Education of the American Medical Association. This booklet provides information relating to other common screening tests used in the school health program.

CHRONIC CYSTIC MASTITIS AND CONTRACEPTION

To the Editor:—*Several years ago in* The Journal, *Dec. 30, 1950, page 1602, in the Queries and Minor Notes section, it was stated in answer to a question that the use of a diaphragm for contraceptive purposes was inadvisable in the presence of chronic cystic mastitis because resultant ovarian stimulation might cause cancer. Would this opinion be rephrased in the light of present evidence?*

M.D., Missouri.

Answer.—The answer to this question remains the same for the following reasons. In experimental animals it has been shown that estrogens possess carcinogenic activity, giving rise to tumors of the breast and uterine cervix. It has been known for some time that the female breast undergoes cyclic changes in response to ovarian hormones (Rosenburg, *Virhow's Arch. f. Path. Anat.* **261**:256, 1925). Chronic cystic mastitis (microscopically diagnosed) is due to unopposed estrogen effect or poor lutein secretion and is treated by progesterone (Womack, personal communication; Geschickter, Diseases of Breast, Philadelphia, J. B. Lippincott Company, 1943). Evidence presented by Geschickter (p. 237) implies that chronic cystic mastitis is hormonal in origin and that the disease occurs only when the cyclic changes are present. It is not found in the male breast or during adolescence or pregnancy. According to Cheatle and Cutler (Tumors of Breast, London, Edward Arnold & Co., 1931), approximately 20% of all mammary cancers have their onset in the changes of chronic cystic mastitis. Warren (*Surg. Gynec. & Obst.* **71**:257, 1940) has confirmed this observation. Sommers and Lombard (*A. M. A. Arch. Path.* **56**:462, 1953) found that 87% of women who died of cancer of the breast had hyperplastic ovarian cortical stroma at autopsy. Both ovaries and adrenals were normal or atrophic in less than 3% of cancer cases. Endometrium and uninvolved breast epithelium were also frequently hyperplastic, accompanying breast cancer. The few cervical specimens available usually showed estrogen effects even in the postmenopause cancer cases. Synthesis of the observations supported the idea of presence of a prolonged estrogenic stimulation of endometrium and breast in the background of about two-thirds of the breast cases. Either ovarian stroma or adrenal cortex, or both, were thought to produce the estrogen, which was concluded to be as important in the development of the human breast cancer as has been shown in rodent mammary cancer (Sommers, *Lab. Invest.* **4**:160, 1955). Prevention of conception (not by diaphragm alone) may extend the prolonged estrogen effect and thus, in a susceptible individual, increase the risk of breast or cervix cancer. Sexual stimulation not resulting in pregnancy for long periods increases the incidence of functional disturbances of the female genital tract, namely, cervicitis, abnormal bleeding, and pelvic congestion. In studies of cervical tissue associated with carcinoma in situ in the same patient, it appears that basal cell hyperactivity, atypia, and epidermidalization are increased in these patients. Therefore, one concludes that contraception is not wise in patients affected with cystic mastitis. Pregnancy would be good therapy. It is not meant to intimate that a diaphragm has any direct affect on the cervix. The contention is, from evidence submitted, that preventing pregnancy has the deleterious effect.

Answer.—There is not sufficient evidence to indicate that a diaphragm pessary could indirectly influence preexisting chronic cystic mastitis. Even though the incidence of malignancy of the breast may be somewhat higher in those patients in whom chronic cystic mastitis has been present, the use of a diaphragm pessary seems rather far removed as a possible causal agent. Issue on this point is more in the realm of polemics than in that of deduction from factual data.

BOWEL IRREGULARITY

To the Editor:—*A woman, 69 years old, has suffered from chronic constipation since she was a small girl. She was then given epsom salt, and later she used a variety of such cathartics as mineral oil, cascara, and phenolphthalein. Recently she has taken a sodium phosphate laxative every three days. Now, aside from the constipation, she does not have a formed stool but water is always present with much gas. She is well nourished, in good physical condition, and not overweight. What could be suggested in way of a diet for this woman? How can the cathartic habit be stopped?*

Burton G. McGarry, M.D., Sarasota, Fla.

Answer.—Until proved otherwise, bowel irregularity indicates cancer of the rectum or distal colon, whether there is a past history of cathartic abuse or not. It is therefore assumed that this

woman has had a thorough investigation of the large intestine, including rectal examination, proctosigmoidoscopy, and barium enema, and that findings in these studies were negative. She has to be weaned from her purgatives and enemas. To achieve this, it will be necessary to brainwash her on the subject of bowel habits along the line that the old belief in intestinal toxemia from chronic constipation is no longer tenable but that it will be necessary to prevent mechanical damage to the rectum and anal sphincter by inspissated feces. The diet will need supervision, and attention must be given to adequate consumption of water and roughage. All purgatives and enemas should be withdrawn. The stool should be prevented from becoming hard and impacted. Mineral oil emulsion is somewhat out of favor at present because of its interference with vitamin absorption, but, used carefully and for short periods of time in an alert patient who has no difficulty in swallowing, it is still of great value. At first, one tablespoonful nightly can be given and, later, one tablespoonful at bedtime if no bowel movement has occurred on that day. With the addition of a water-retaining substance, such as agar-agar, psyllium seed, or methylcellulose, the amount of mineral oil can be decreased. At start of therapy the bowel movements will doubtless be irregular, but, with the help of an occasional enema and dose of cascara sagrada, this difficulty will be overcome; these should only be taken by order of the physician. The essential point, however, will be to convince the patient that a daily bowel movement is not essential for health, that she can go without one for days without ill effect, and that if she follows instructions normal colonic peristalsis will return, even at her age.

ANTIBIOTICS AND LONGEVITY

To the Editor:—*It has been stated that the greatest factor in longevity is heredity. Have the antibiotic drugs changed this viewpoint or materially contributed toward longevity as such?*

Jules Magnette, M.D., Reno, Nev.

Answer.—Since the antibiotics have been in general use for little more than half of a single generation, the answer to this question must be based on speculation and analogy. They will probably pull through childhood a number of individuals who have inherently weak constitutions and who will not live out the normal span of adult life. Ploetz' study of the infant mortality in the royal and princely families of Europe, where every child has had the advantage of the best care that the state of science at the time of his birth could furnish, showed a close relation between the length of the father's life and the child's mortality. If the parents were short-lived, the child evidently inherited the same weak constitution and his own expectation of life was not so good. This survival of inherently weak children who will not live to advanced age will tend, to some extent, at least, to counterbalance the prolongation of life of elderly persons through a lower death rate from pneumonia and other familiar causes. At present, an "educated guess" might be that the antibiotics will lengthen the lives of some individuals, because of their effect on the infectious diseases, that they will not be of much effect on the degenerative diseases, in which the influence of heredity is more important, and that the net result may be very little change in the average longevity of the race.

STEROID MEDICATION AND RHEUMATIC FEVER

To the Editor:—*An 8-year-old girl with rheumatic fever was treated with a large dosage of aspirin and 15 mg. of prednisolone daily. She has also received 200,000 units of penicillin daily, by mouth. Fever and swollen and painful joints subsided with this therapy. After consultation the prednisone was gradually withdrawn, but then the symptoms reappeared. The patient has been hospitalized twice for blood, electrocardiographic, and chest examinations. So far, there are no cardiac symptoms. The present medication includes large dosages of aspirin plus 5 mg. of prednisolone daily. This treatment keeps her symptoms only partially checked. She has always shown marked improvement after the prednisolone is administered. Should a maintenance dosage of prednisolone be continued, or should this drug be withdrawn? Please give suggestions for treatment.*

M.D., Virginia.

Answer.—The use of steroids in the treatment of acute rheumatic fever, according to most workers in the field, depends on whether carditis is present. If polyarthritis is the only major manifestation and if evidence of a beta-hemolytic streptococcic infection suggests that the disease is acute rheumatic fever rather than rheumatoid arthritis, lupus erythematosus, or other diseases associated with polyarthritis, the first therapeutic measure taken in addition to bed rest is eradication of the Streptococcus. Adequate doses of penicillin are given for 10 days, preferably parenterally, according to the dosage schedules recommended by the American Heart Association. Thereafter, the patient is maintained on prophylactic medication according to the AHA-recommended regimens (1,200,000 units of benzathine penicillin G given intramuscularly every four weeks, or 250,000 units of penicillin G given orally twice daily, or 0.5 Gm. of sulfadiazine given twice daily). Repeated throat cultures should then be negative for beta-hemolytic streptococci. Symptomatic relief is afforded by the use of salycilates, starting with a dose of 1 grain (0.06 Gm.) per pound of body weight in

24 hours (in divided doses) for the first two days (150-grain [9.72-Gm.] maximum daily dose), then ⅔ grain per pound of body weight in 24 hours for five days, and finally ½ grain per pound of body weight in 24 hours for the duration of therapy. Therapy is continued for several weeks after all physical and laboratory findings (such as erythrocyte sedimentation rate, white blood cell count, and C-reactive protein precipitation) of activity of the rheumatic process return to normal values. In the usual case this entails a six-week period of therapy. Steroids are usually not used unless carditis is present. In addition to therapy for symptomatic relief, a high-vitamin, high-protein diet is recommended. The patient is kept at bed rest until therapy with salycilates has been discontinued and all signs of the rheumatic process have returned to normal. He is then allowed increasing activity, and, if in two to three weeks no signs of rheumatic disease become evident, he is allowed full, unrestricted activity, provided carditis was not manifest. The recurrence of joint manifestations in acute rheumatic fever is not uncommon if suppressive therapy (salycilates or steroids) is discontinued too early. However, a six-week course of therapy followed by reappearance of polyarthritis without evidence of carditis on discontinuing therapy suggests the possibility that the disease is other than rheumatic fever, unless evidence of reinfection with beta-hemolytic streptococci is obtained.

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WEIGHT REDUCTION BY COATING THE FOOD

To the Editor:—*Is there any method of lowering the calorie value of ingested food by reducing the dietary efficiency of the gastrointestinal tract? Could this be done by means of some oral medication that would coat the food particles and prevent complete action on them by the digestive fluids or act in some similar manner? It would seem that such a method would be an excellent way to obtain weight reduction in individuals not willing to restrain their dietary intake. A vitamin-mineral supplement could be given between meals to prevent deficiency developing from the medical or chemical absorption-hindering agent.*

J. D. Marshall, M.D., Portland, Ore.

Answer.—To the knowledge of this consultant, a method of weight reduction by coating the food has never been publicized. Mineral oil is the only such substance that comes immediately to mind as being indigestible. The Food and Drug Administration does not permit it in foods, however. Such a method leaves quite a bit to be desired. While it may effect a reduction in weight, no effort is being made to retrain the person in his eating habits. This latter aspect is particularly important if the person is to maintain whatever weight loss is achieved. He certainly will not maintain it by continuing to eat in an accustomed manner. It is seriously questioned whether the continued ingestion of a "coated" diet would be physiologically desirable.

MORPHEA OF THE SCALP

To the Editor:—*The mother of a 4-year-old boy who has morphea of the scalp wishes to know whether the condition will be permanent, what treatment will halt the progress of the disease, and whether the disease should be allowed to take its course. The lesion occupies an area of about 1 by 2 in. in the middle of the scalp.*

Edwin L. Stickney, M.D., Broadus, Mont.

Answer.—The course of morphea, or circumscribed scleroderma, either is chronic, and as such may run a course of 1 to 10 years, or is, occasionally, subacute, and lasts a comparatively short time. As the disease clears up, there is commonly left a thin, inconspicuous, atrophic area. This lesion may be even less conspicuous in the scalp, although the alopecia of the site will probably be permanent. One must be certain that the disease is morphea rather than a congenital defect of the scalp (Behrman, The Scalp in Health and Disease, St. Louis, C. V. Mosby Company, 1952). There is no specific treatment of value for circumscribed scleroderma, although various measures have been recommended. These include massage, bland ointments containing 1% pilocarpine, acetylcholine chloride administered by iontophoresis, and other forms of vasodilatation. In view of the particular location described, the employment of gentle massage and the application of a mild vasodilating type of ointment may be of some small benefit.

PULLING HAIR OUT OF THE HEAD

To the Editor:—*A 2-year-old girl has been pulling hair out of her head for the past several months. Hair is missing from practically the entire back of her head. Please give suggestions on cause and cure.*

Robert M. Stansbury, M.D., Lancaster, Calif.

Answer.—It is assumed that the evidence is definite that the child is pulling out the hair and that this is not a bald area which results from the child's lying excessively in the supine position (as might occur in a severely neglected or retarded child). One would be concerned about emotional factors in the etiology of the symptom described. It could be assumed that for some reason the child's gratification from her relationships with parents and others is insufficient and that she is, in consequence, becoming more preoccupied with her body. There is no specific psychodynamic constellation which produces this symptom. In a child of this age, however, one would be concerned about any re-

cent separation from parents or grandparents, the recent birth of a sibling, excessive pressures in toilet training or feeding, or any other psychologically upsetting circumstance. Any one of these —or a grouping of them—may be present, and treatment should be directed at minimizing these factors while providing gratifying play experiences for the child.

MICRO-ORGANISMS IN TOBACCO

To the Editor:—*Has there been any investigation of the type of micro-organisms found in the tobacco of cigarettes and of whether these are a source of infection to the respiratory system, the gastrointestinal tract, or other systems?*

M.D., New York.

Answer.—There is an abundant flora of micro-organisms in the tobacco leaf (Frankenburg, *Advances Enzymol.* **6**:309, 1946; **10**:325, 1950) as in most organic material. There is no record in the literature of any that are harmful to man or other animal species. The process of combustion would destroy any living organisms in smoked tobacco. Among the number of references to the bactericidal effects of tobacco smoke are reports by the following workers: Appleton and Lehmer (*Dental Cosmos* **70**:1111, 1928), Miller (*Independ. Pract.* **5**:284, 1884), Parfentjev, reported by Hammond (*Cancer* **7**:1100, 1954), Tassinari (*Centralbl. f. Bakteriol. u. Parasitenk.* **4**:449, 1888), and Turkheim (*J. Dent. Res.* **31**:326, 1952).

STERILIZATION OF SIGMOIDOSCOPES

To the Editor:—*Should sigmoidoscopes be sterilized between patients, or is washing with soap and water adequate? If sterilization is necessary, would any germicidal liquid agent be considered sufficient?*

M.D., Louisiana.

Answer.—Sigmoidoscopes should be sterilized before they are utilized for the purpose of examining the terminal portion of the colon. Sterilization is accomplished best by immersing the instrument in boiling water.

VITAMIN E FOR "HOT FLASHES"

To the Editor:—*In January, 1958, a 42-year-old woman had a total hysterectomy and bilateral salpingo-oophorectomy. There was an ovarian cyst on the right side which contained an adenocarcinoma, grade 2. She received 30 deep x-ray treatments. Is there any medication, under the circumstances, which could be given to alleviate the intensity of "hot flashes"?*

C. E. Cassaday, M.D., Mt. Vernon, Ohio.

Answer.—The use of alpha tocopherol (vitamin E), 25 mg. given three times a day, is recommended. Estrogens are definitely contraindicated in individuals who have been treated for carcinoma, due to the fact that they may activate dormant cells to malignant phases. Alpha tocopherol causes no such stimulation of dormant cells which may have this propensity. This consultant has had some success with this medication; it is recommended with the belief that it has definite value in diminishing or causing absence of hot flashes.

NEOSTIGMINE FOR A PREGNANCY TEST

To the Editor:—*Please advise as to the current status of the use of neostigmine methylsulfate as a pregnancy screening test. Have there been any reports of its use precipitating miscarriages?*

M.D., Massachusetts.

Answer.—The administration of neostigmine methylsulfate (1:2,000) daily for three consecutive days will usually be followed by uterine bleeding within three days if the patient is not pregnant. This procedure applies only to delayed menstruation in women who have had a normal menstrual history up to the last period. It does not apply either to early or to prolonged amenorrhea due to endocrine dysfunction or to local organic changes. There is no evidence that this drug precipitates miscarriages.

CLEANING EYE GLASSES

To the Editor:—*What is the best way to clean eye glasses? Please comment on the silicone treated papers, "special" cleaning fluids, and plain soap and water.*

M.D., California.

Answer.—Silicone treated papers are not usually recommended for general use, since silicone itself will remove any nonreflective coatings that may have been applied to the lenses. No harm can come to any lenses from this paper, however, if they have not been so coated. Soap and water continues to be an excellent cleaner, provided a mild hand soap is used. Stronger soaps might affect some of the trims that are often applied to women's frames. Several good cleaning fluids, available in any optical office, also do an excellent job of cleaning. These contain a mild alcohol solution, which takes off most spots and dirt.

PREVENTING BLOOD COAGULATION

To the Editor:—*How many units (on the average) of heparin are required per 100 ml. of whole blood to prevent coagulation?*

M.D., New York.

Answer.—The usual amount of a commercial preparation of heparin used to prevent the coagulation of collected blood in glass is 4 mg. per 100 ml. (1 mg. is equal to 10 units). If blood is collected in a plastic or silicone-coated container, a smaller amount will be needed to keep the blood noncoagulable.